AN OPEN-LABEL, SINGLE-ARM, PHASE 1 STUDY OF PHARMACOKINETICS, SAFETY AND ANTI-TUMOR ACTIVITY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

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Short Title: A PHASE 1 STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	27 January 2020	N/A
Amendment 01	26 May 2020	• Updated the requirement of keeping fasted after dosing on Cycle 1 Day -9, Cycle 1 Day 22: reduced the duration time of fasting to 2 hours after dosing. • Added FSH sample volume in table 3 to keep consistent with protocol text. • "Leukocytes esterase" is updated to "leukocytes esterase/leukocytes" to add leukocytes as an alternative analyte to accommodate standard laboratory testing capabilities. • Update the protocol based on the new protocol template (15 May 2020).

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A PHASE 1 STUDY OF TALAZOPARIB MONOTHERAPY IN CHINESE PARTICIPANTS WITH ADVANCED SOLID TUMORS

Rationale

The purpose of the study is to obtain the pharmacokinetic (PK) profile of talazoparib after both single-dose and multiple dose administration as monotherapy in Chinese participants with advanced solid tumors to support potential registration of indications in China. Safety and activity of talazoparib will also be assessed as the secondary objectives in this study.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To characterize the single and steady-state pharmacokinetics (PK) of single-agent talazoparib.	Not applicable.	• Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and V_z/F and $t_{½}$, and AUC_{inf} as data permit. • Multiple Dose (MD) - C_{max}, T_{max}, C_{min}, AUC_{τ}, CL/F, R_{ac} ($AUC_{\tau}/AUC_{sd,\tau}$) and R_{ss} ($AUC_{\tau}/AUC_{sd,inf}$) as data permit.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the overall safety profile. • To assess preliminary evidence of anti-tumor activity of single-agent talazoparib.	Not applicable.	Safety: • Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to talazoparib. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing. • Vital signs and ECG. • Concomitant medication use. Efficacy: • Unconfirmed objective response rate (ORR). • Duration of response (DOR).

Overall Design

This study is a Phase 1 study to evaluate the PK and safety of single agent talazoparib 1 mg Once Daily (QD) in Chinese adult participants with advanced solid tumors who are resistant to standard therapy or for whom no standard therapy is available.

Study treatment will be given once daily in 28-day cycles. To understand the single-dose safety and single-dose PK assessments of talazoparib, a lead-in period preceding the continuous daily doses will be included. In the 9-day lead-in period, a single lead-in dose will be given on Day -9 and PK samples will be collected at pre-dose and 0.50, 1, 2, 4, 8, 24,

48, 96, 168 and 216 hours post dose. No talazoparib will be administered during the interval between the lead-in single dose and Day 1 of the first cycle. Additionally, to characterize the steady state PK profile, serial PK samples after multiple doses will be collected on Day 22 of the first cycle at pre-dose, 0.50, 1, 2, 4, 8, 24 hours post dose.

An End of Treatment visit will be performed for participants if the specified assessments are not completed in the last week (last 6 weeks for tumor assessments).

Number of Participants

A maximum of approximately 15 participants will be enrolled to study intervention such that approximately 12 evaluable participants complete the study.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

A single dose of talazoparib 1 mg is administered on Day -9, then continuous dosing will begin from C1D1. Participants will be given talazoparib 1 mg orally QD until disease progression, death, unacceptable toxicity or withdrawal of consent. Dose modifications and reductions for talazoparib are to occur according to the Section 6.6.

Data Monitoring Committee or Other Independent Oversight Committee

No.

Statistical Methods

A maximum of approximately15 patients are needed. Pharmacokinetic parameters and plasma concentration data will be summarized as the primary analysis for this study. In addition, safety data including adverse events (AE), laboratory abnormalities and electrocardiogram measurements (ECG), as well as efficacy information reflected by objective response (OR) and duration of response (DOR) will also be summarized and estimated.

1.2. Schema

Not applicable.

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.

Schedule of Activities 1 (Overall Study)

Visit Identifier[a] Visit or Assessment window [days] unless otherwise noted.	Screening[b] (≤28 days prior to Lead-in)	Lead in	Cycle 1			Cycle 2-4		Cycle ≥5	End of Treatment[d]	Follow- up[e] 28 days post dose	Early Termination/ Discontinuation[f]
		Day -9	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1			
Visit Window				±1	±1	±2[c]	±2	±2		+7	
Informed consent[g]	X										
Tumor history	X										
Medical history	X										
Physical examination	X	X	X			X		X	X		X
Baseline signs and symptoms[h]	X										
Height	X										
Weight	X	X	X			X		X	X		X
Vital signs[i]	X	X	X	X		X	X	X	X	X	X
Performance status[j]	X		X			X		X	X		X
Laboratory											
Hematology[k]	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry[l]	X	X	X	X		X		X	X	X	X
Urinalysis[m]	X								X	X	X
Pregnancy test[n]	X	X				X		X	X	X	X
FSH[o]	X										
Virus test (HBV/HCV/HIV)[p]	X										

Visit Identifier[a] Visit or Assessment window [days] unless otherwise noted.	Screening[b] (≤28 days prior to Lead-in)	Lead in	Cycle 1			Cycle 2-4		Cycle ≥5	End of Treatment[d]	Follow- up[e] 28 days post dose	Early Termination/ Discontinuation[f]
		Day -9	Day 1	Day 15	Day 22	Day 1	Day 15	Day 1			
Visit Window				±1	±1	±2[c]	±2	±2		+7	
Contraception check[q]	X	X	X			X		X	X	X	X
(12 lead) ECG[r]	X	X	X			X		X	X	X	X
Registration and Treatment											
Registration[s]	X										
Study intervention dispensing		X	X			X		X			
Study intervention[t]		X	X	→	→	→	→	→			
Tumor assessments											
CT or MRI scan or equivalent[u]	X					X (see details in the footnote)			X		X
Other clinical assessments											
Serious and non-serious adverse event monitoring[v]	X	→	→	→	→	→	→	→	→	→	→
Concomitant treatment(s)[w]	X	→	→	→	→	→	→	→	→	→	X
Other samplings											
Pharmacokinetics[x]			Refer to Pharmacokinetics Sampling Schema								

Abbreviations used in this table may be found in Appendix 11.

a. Day relative to start of study intervention (Day 1).

b. Screening: To be obtained within 28 days prior to Cycle 1 Day -9 (C1D-9).

c. For Cycle 2 Day 1 (C2D1), "±2 days" window is not applicable. Window for C2D1 is "±1 day".

d. End of Treatment Visit: Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).

e. Follow-up: At least 28 calendar days, and no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, vital signs, safety lab tests, ECG, contraception check and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. Pregnancy test will be performed for women of childbearing potential only.

f. Early Termination/Discontinuation: Applies only to participants who are enrolled and then are prematurely withdrawn from the study. Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments).

g. Informed Consent: Must be obtained prior to undergoing any study-specific procedures. Procedures performed as standard of care prior to signed and dated informed consent document (ICD), and within the 28 day screening window may be used for study eligibility.

h. Baseline Signs & Symptoms: Patients will be asked about any signs and symptoms experienced within the 14 days prior to PK lead-in dose. Clinically significant baseline signs and symptoms will be recorded as part of the Medical History.

i. Vital Signs: Systolic and diastolic blood pressure (BP), pulse rate, respiratory rate and temperature at scheduled time points; BP and pulse rate to be recorded in sitting position.

j. Performance Status: Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 8.

k. Hematology: No need to repeat on C1D-9 if baseline assessment performed within 7 days prior to that date. Additional hematology may be performed as clinically indicated. Frequency should be increased as clinically indicated to monitor neutropenia, thrombocytopenia, and anemia. See Assessments section for Laboratory Tests list.

l. Blood Chemistry: No need to repeat on C1D-9 if baseline assessment performed within 7 days prior to that date. Additional chemistries may be performed as clinically indicated. See Assessments section for Laboratory Tests list.

m. Urinalysis: Dipstick is acceptable. Microscopic analyses if dipstick abnormal. No need to repeat on C1D-9 if baseline assessment performed within 7 days prior to that date. Additional urinalysis may be performed as clinically indicated. See Assessments section for Laboratory Tests list.

n. Pregnancy Test: For Woman of Childbearing Potential (WOCBP) only, see protocol Section 10.4 for details.

o. FSH: For confirmation of postmenopausal status only.

p. Virus (HBV/HCV/HIV) test: Perform within 28 days prior to the first study treatment, including HBV (HBsAg and HBcAb), HCV antibody, and HIV antibody.

q. The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly. Also, it is the opportunity to assess changing potential to father/bear children and allows for altering contraception if new disease contraindicates a selected method of contraception or if nonchildbearing status is achieved.

r. 12-Lead ECG: Predose on Day -9 will be used as baseline, three consecutive 12-lead ECG will be performed approximately 2 minutes apart to determine PR interval and the mean QTc interval. At screening as well as each scheduled ECG evaluation on treatment, a single 12-lead ECG will be performed. If there is a potential significant change, the investigator can provide additional measurements as appropriate. All ECGs scheduled on treatment should be performed pre-dose. When coinciding with blood sample draws for PK or other safety lab tests, ECG assessment should be performed prior to blood sample collection. Additional ECGs may be performed as clinically indicated. See protocol Section 8.2.3 for details and additional requirement for special case.

s. Registration: Assign patient number.

t. Study Treatment: Described in the Study Treatments section. A single dose of talazoparib is administered on Day -9, then continuous dosing will begin from C1D1.

u. Tumor Assessments: Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans. A brain MRI or CT is to be performed at Screening/baseline to evaluate participants for presence/absence of brain metastases. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. CT or MRI scans to be done on D29 (±7 days window) and every 8 weeks (±7 days window) thereafter for the initial 12 cycles regardless of any dose interruptions or dose delays. After completion of Cycle 12 (at the beginning of Week 45), tumor assessment will be done per local standard practice. Tumor assessments should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation. Given the exploratory nature of the efficacy endpoint, confirmation of response (complete response [CR]/partial response [PR]) is not required. As clinically indicated, CT/MRI will be repeated by investigator's discretion. Assessment of response will be made using RECIST version 1.1.

v. Adverse Event (AE) Assessments: AEs should be documented and recorded at each visit using the NCI CTCAE version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last investigational product administration. If the participant begins a new anti-cancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.

w. Concomitant Treatments: all concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF. All concomitant treatments and nondrug interventions received by participants from 28 days before first dose are considered as Prior/Concomitant Therapy.

x. PK Sampling: Refer to Pharmacokinetics Sampling Schema.

Schedule of Activities 2 (Pharmacokinetic Sampling Schema)

Study Day	Lead in										Cycle 1								
	Day -9						-8	-7	-5	-2	Day 1	21	22[c]						23
Hours Before/After Dose	**0[a]**	**0.5**	**1**	**2**	**4**	**8**	**24**	**48**	**96**	**168**	**216[a]**	**0[a]**	**0[a]**	**0.5**	**1**	**2**	**4**	**8**	**24[a]**
Study treatment administration	X										X	X	X						X
PK blood sampling[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviation: PK = pharmacokinetic.

a. Pre-dose sample collection. Study treatment administration should be after the PK blood sampling.

b. Blood will be collected for PK sampling of talazoparib. In lead in phase, after a single dose of tarazoparib, samples at pre-dose and 0.5, 1, 2, 4, 8 hour on Day -9 of first Cycle. After that, 24, 48, 96, 168 hour post dose samples will be collected through D-8 to D-2 of first cycle. Pre-dose sample will be collected on C1D1 dosing as 216 hour post dose sample. Serial PK samples after multiple dose will be collected on C1D22 at pre-dose, 0.5, 1, 2, 4, 8 hour. Pre-dose samples will be collected on C1D21, C1D23. On days of clinic visits, talazoparib should be taken at the clinic after completion of pre-dose sampling and assessments.

c. In the event of any dose interruption or reduction before Cycle 1 Day 22, the intensive PK sampling shall be postponed to Day 1 or 15 of next cycle but no later than Cycle 4 if consecutive 20 days dosing prior to PK sampling is achieved.

2. INTRODUCTION

Talazoparib tosylate (PF-06944076, formerly BMN 673 or MDV3800), which is cytotoxic to human cancer cell lines harboring gene mutations that compromise DNA repair, an effect referred to as synthetic lethality, by inhibiting Poly(Adenosine Diphosphate-Ribose) Polymerase (PARP) catalytic activity and trapping PARP protein on DNA, thereby preventing DNA repair, replication, and transcription.[1,2,3]

Talazoparib has been approved in United States, European Union and other countries for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Other potential indications, such as metastatic castration resistant prostate cancer (mCRPC), are currently being investigated.

2.1. Study Rationale

The purpose of the study is to obtain the pharmacokinetic (PK) profile of talazoparib after both single-dose and multiple dose administration as monotherapy in Chinese participants with advanced solid tumors to support potential registration of indications in China. Safety and activity of talazoparib will also be assessed as the secondary objectives in this study.

2.2. Background

Cancer incidence and mortality are rapidly growing worldwide. GLOBOCAN 2018 estimated that there will be 18.1 million new cases (17.0 million excluding nonmelanoma skin cancer (NMSC)) and 9.6 million cancer deaths (9.5 million excluding NMSC) worldwide in 2018. With the world's largest population, about a fifth of all global cancer cases occur in China,[4] and cancer has become the leading cause of death in the country in recent years.[5] Despite a marked increase in 5-year survival from all cancers combined and several major cancers over the last decade in China, survival for many major cancers in the most recent period studied remained lower than in many developed countries.[6] Cancer represents a disease are with high unmet medical need in China and the discovery and development of new anti-cancer therapies effective is urgently needed.

2.2.1. Clinical Overview

Clinical Pharmacology Overview

Talazoparib plasma exposure is dose proportional in the dose range of 0.025 mg to 2 mg QD suggesting linear PK. Talazoparib absolute bioavailability is at least 54.6% based on excretion of unchanged talazoparib in urine. After administration of a single 1 mg dose of talazoparib to cancer patients, the median Time to Reach Maximum Plasma Concentration (T_{max}) ranged from 0.5 to 2.0 hours across studies. Administration of talazoparib with food (a high-fat, high-calorie meal) had no impact on the total exposure (AUC_{inf}) while the maximum plasma concentration (C_{max}) was reduced by 46%. The reduction in the rate of absorption with food is not expected to be clinically relevant as efficacy is generally driven by total exposure. Therefore, talazoparib can be taken with or without food.

Talazoparib undergoes minimal hepatic metabolism. Based on population PK analysis, there is no effect of mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1.0 to 1.5 ULN and any AST) on talazoparib exposure. No dose adjustment is necessary for patients with mild hepatic impairment.

Talazoparib is eliminated slowly with a mean terminal plasma half-life of 89.8 hours. Talazoparib accumulates after 1 mg QD dosing with a median accumulation ratio ranging from 2.33 to 5.15, consistent with its terminal half-life. Population PK analysis showed that talazoparib CL/F was 6.45 L/h.

Excretion of unchanged talazoparib in urine is the major route of elimination accounting for 54.6% of the administered dose. Study MDV3800-01 was conducted to investigate the effect of mild, moderate, and severe renal impairment on the PK of talazoparib following daily oral dosing of 0.5 mg talazoparib for 22 days in patients with advanced solid tumors. No trend was observed in the geometric mean f_u in plasma with worsening renal function. The adjusted geometric means for total talazoparib exposure (AUC_{0-24}) increased by 12.2%, 43.0%, and 163.3% after multiple doses with mild (*eGFR ≥60 and ≤89 mL/min/1.73 m^2*), moderate (*eGFR ≥30 and ≤59 mL/min/1.73 m^2*), and severe renal impairment (*eGFR ≥15 and ≤29 mL/min/1.73 m^2*), respectively, relative to patients with normal renal function (*eGFR ≥90 mL/min/1.73 m^2*) as assessed by Analysis of Variance (ANOVA) analyses comparing the categorical renal function groups defined by BSA-normalized Estimated Glomerular Filtration Rate (eGFR). Peak talazoparib exposure based on C_{max} increased by 11.1%, 31.6%, and 89.3% after multiple doses with mild, moderate, and severe renal impairment, respectively, relative to patients with normal renal function as assessed by ANOVA analyses comparing the categorical renal function groups defined by BSA-normalized eGFR. Population PK analysis showed that talazoparib CL/F is reduced by 14.4% and 37.1% in patients with mild renal impairment (CLcr 60 to 89 mL/min) and moderate renal impairment (30 mL/min ≥ CLcr <60 mL/min), corresponding to 17% and 59% increases in AUC respectively, compared to that of patients with normal renal function (CLcr ≥90 mL/min), which was consistent with the results in the renal impairment study. No dose adjustment is recommended for patients with mild renal impairment. For patients with moderate renal impairment, the talazoparib dose in the monotherapy setting should be reduced from 1 mg QD to 0.75 mg QD. For patients with severe renal impairment (15 mL/min ≤ CL_{cr} <30 mL/min), the talazoparib dose should be reduced to 0.5 mg QD.

Based on in vitro studies, talazoparib is a substrate for the efflux transporters P-gp and Breast Cancer Resistance Protein (BCRP). Data from the recently completed Drug-Drug Interaction (DDI) Study C3441004 (MDV3800-04) in patients with advanced solid tumors indicated that coadministration of multiple daily doses of strong P-gp inhibitor itraconazole 100 mg twice daily with a single 0.5 mg talazoparib dose increased talazoparib AUC_{inf} and C_{max} by approximately 56% and 40%, respectively, relative to a single 0.5 mg talazoparib dose administered alone. The increase in the talazoparib mean terminal half-life when talazoparib was administered with itraconazole compared to when talazoparib was administered alone (118.5 hours vs 101.3 hours) was minor, suggesting that the increase in talazoparib exposure when coadministered with itraconazole is predominantly due to an increase in talazoparib

bioavailability with minor effect on elimination. Consistent with findings from Study C3441004, population PK analysis indicated that concomitant administration of strong P-gp inhibitors with talazoparib increased talazoparib exposure by 44.7% relative to talazoparib administered alone. If concomitant use of strong P-gp inhibitors during treatment with talazoparib is unavoidable, the talazoparib dose should be reduced from 1 mg QD to 0.75 mg QD. Data from Study C3441004 indicated that coadministration of multiple daily doses of a strong P-gp inducer, rifampin 600 mg, with a single 1 mg talazoparib dose, increased talazoparib C_{max} by approximately 37% whereas AUC_{inf} was not affected relative to a single dose of talazoparib 1 mg administered alone.

Exposure-efficacy analysis showed that higher talazoparib exposure in the Phase 3 EMBRACA study (Study 673-301; C3441009) is associated with longer PFS in patients with germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer. Exposure-safety analyses based on pooled data from the Phase 2 ABRAZO study (Study 673-201; C3441008) and EMBRACA showed that higher talazoparib exposure is also associated with a higher risk for Grade 3 or higher anemia and thrombocytopenia, and a trend for association between higher talazoparib exposure and Grade 3 or higher neutropenia although this relationship was not statistically significant. These findings support using the Maximum Tolerated Dose (MTD) of 1 mg QD in the monotherapy setting in advanced breast cancer patients as the recommended dose for talazoparib treatment and the proposed dose modification guidelines as an effective approach for management of AEs.

Clinical Safety and Efficacy

As of 30 September 2019, approximately 1212 participants and 18 healthy volunteers have received talazoparib at doses up to 2 mg QD in company-sponsored clinical studies in hematologic malignancies and solid tumors. The majority of available efficacy and safety data was obtained from studies in solid tumors. A phase 1 study in participants with advanced or recurrent solid tumors defined the MTD of talazoparib as 1 mg QD. Data from this study demonstrated objective responses and/or clinical benefit in participants with breast, ovarian/peritoneal, and pancreatic cancer; SCLC; and Ewing sarcoma.

Aggregate safety data from 5 open-label, including 1 randomized, company-sponsored clinical studies (PRP-001, 673-201, EMBRACA, MDV3800-13, and MDV3800-14; N = 502 patients) evaluating talazoparib monotherapy in solid tumors at the proposed dose of 1 mg QD as of 30 September 2019, provide the basis for the reported treatment-emergent adverse events (TEAEs). TEAEs of all causality reported in ≥20% of participants administered single-agent talazoparib 1 mg QD are related to myelosuppression (anemia, neutropenia), GI toxicity (nausea, diarrhea, vomiting, constipation, and decreased appetite), fatigue, headache, and alopecia. TEAEs of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 severity in ≥5% of participants were related to myelosuppression. Twenty (20) of 502 participants (4.0%) in the Talazoparib 1 mg QD Population permanently discontinued study drug due to a TEAE. The events that led to study drug permanent discontinuation were anemia (3 participants), increased alanine aminotransferase (ALT, 2 participants), and accidental overdose, increased aspartate

aminotransferase (AST), bradycardia, metastatic breast cancer, cerebral hemorrhage, dyspnea, glioblastoma multiforme, headache, metastases to meninges, muscular weakness, neutropenia, obstructive airways disorder, thrombocytopenia, transient ischemic attack, and vomiting (1 participant each). Among the 502 participants in the Talazoparib 1 mg QD Population, 63.9% had a TEAE that led to dose reduction and 61.2% had a TEAE that led to dosing interruption. The most common TEAEs that led to dose reduction or interruption were associated with myelosuppression.

Efficacy data from 3 Sponsor-initiated studies (PRP-001, Studies 673-201, and 673-301) evaluating talazoparib in participants with advanced or metastatic breast cancer are included in this investigator brochure. In the Phase 1 first-in-human study (Study PRP-001 [C3441007]) in participants with advanced or recurrent solid tumors, a total of 110 participants were treated at a range of talazoparib doses (0.025-1.1 mg QD). Data from this study demonstrated objective responses and/or clinical benefit in participants with breast, ovarian/peritoneal, and pancreatic cancer; small-cell lung cancer (SCLC); and Ewing sarcoma.

In an open-label Phase 2 study (Study 673-201, [C3441008, ABRAZO]) of talazoparib in participants with germline BRCA-mutated locally advanced or metastatic breast cancer, 83 participants were treated with talazoparib 1 mg QD across 2 cohorts. Cohort 1 enrolled 49 participants (48 treated) who had a partial response (PR) or complete response (CR) to a prior platinum- containing regimen for metastatic disease with disease progression >8 weeks following the last dose of platinum. Cohort 2 enrolled 35 participants who received 3 or more prior chemotherapy regimens and no prior platinum therapy for metastatic disease. Cohort 1 had an objective response rate (ORR) of 20.8% (95% CI: 10.5, 35.0) including 2 CRs (4.2%). Cohort 2 had an ORR of 37.1% (95% CI: 21.5, 55.1). Median duration of response (DOR) was 4.9 months (interquartile range [IQR]: 2.8, 7.1) in Cohort 1 and 4.2 months (IQR: 3.2, 5.6) in Cohort 2.

In the pivotal randomized Phase 3 study (Study 673-301, [C3441009, EMBRACA]) of talazoparib versus physician's choice treatment (PCT) in participants with germline BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, 431 participants overall were randomized in a 2:1 ratio to receive talazoparib 1 mg QD (n = 287) or 1 of 4 PCTs (n = 144) reflecting the standard of care in this disease setting (capecitabine, eribulin, gemcitabine, or vinorelbine). In this study, talazoparib demonstrated significantly prolonged progression-free survival (PFS) by blinded independent central review (BICR) assessment when compared to PCT. Median PFS by BICR in the talazoparib arm was 8.6 months (95% CI: 7.2, 9.3) compared to 5.6 months (95% CI: 4.2, 6.7) in the PCT arm.

Talazoparib is currently being evaluated in mCRPC. An ongoing Phase 2 study [C3441006, TALAPRO-1] is evaluating talazoparib in men with DNA repair defects and mCRPC who previously received taxane-based chemotherapy and progressed on at least 1 novel hormonal agent (enzalutamide and/or abiraterone acetate/prednisone). In addition, an ongoing Phase 3, randomized, double-blind, placebo-controlled study [C3441021, TALAPRO-2] is evaluating

talazoparib in combination with enzalutamide in mCRPC participants with and without DNA damage repair deficiency mutations. The effectiveness of talazoparib is also under investigation for the neoadjuvant treatment of germline BRCA 1/2 mutation participants with early triple-negative breast cancer, and in combination with the anti-programmed death ligand 1(PD-L1) checkpoint inhibitor, avelumab, for the treatment of selected solid tumors.

2.3. Benefit/Risk Assessment

Talazoparib has been approved in multiple countries for the treatment of adult patients with deleterious or suspected deleterious gBRCAm HER2-negative locally advanced or metastatic breast cancer. Preclinical studies shown that talazoparib is a highly selective and potent cytotoxic agent in human cancer cell lines and in animal models of tumors harboring mutations that compromise DNA repair pathways. Risk assessment, benefit assessment, as well as overall risk/benefit analysis are provided separately as below.

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 single reference safety document (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: Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML), and second primary malignancies. These risks represent adverse events of special interest for talazoparib (see Section 8.3.8).	The potential risks are based on 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. Second primary malignancies may be identified with imaging provided for tumor assessment. Investigator can provide unplanned assessment as clinically indicated.

2.3.2. Benefit Assessment

The activity of talazoparib as monotherapy and in combination with other agents is being evaluated in multiple indications. The benefit of talazoparib for individual participants with solid tumors may include:

- Participants in this study will contribute to the process of developing a new therapy in an area of unmet need in China.
- Potential benefit of receiving talazoparib during study duration that may have clinical utility.

- Medical assessment (eg, imaging, physical exams, ECGs, Labs, etc.) associated with study procedures will be provided to explore the benefit/risk profile of the Chinese population in this study.

2.3.3. Overall Benefit/Risk Conclusion

According to the aggregate safety data from 5 clinical studies (PRP-001, 673-201, 673-301, MDV3800-13, and MDV3800-14; N = 502 participants), treatment-emergent adverse events (TEAEs) associated with talazoparib monotherapy in solid tumors at the proposed dose of 1 mg QD are detectable through routine laboratory and clinical monitoring and may be managed with supportive care or dose reductions or interruptions as described in each study protocol.

In PRP-001 [C3441007]) study, a total of 110 participants with advanced or recurrent solid tumors were treated at a range of talazoparib doses (0.025-1.1 mg QD). Data from this study demonstrated objective responses and/or clinical benefit in participants with breast, ovarian/peritoneal, and pancreatic cancer; small-cell lung cancer (SCLC); and Ewing sarcoma.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of talazoparib may be found in the investigator's brochure.

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 tumors.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To characterize the single and steady-state pharmacokinetics (PK) of single-agent talazoparib.	Not applicable.	• Single Dose (SD) - C_{max}, T_{max}, AUC_{last}, AUC_{τ}, CL/F, and V_z/F and $t_{½}$, and AUC_{inf} as data permit. • Multiple Dose (MD) - C_{max}, T_{max}, C_{min}, AUC_{τ}, CL/F, R_{ac} ($AUC_{\tau}/AUC_{sd,\tau}$) and R_{ss} ($AUC_{\tau}AUC_{sd,inf}$) as data permit.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the overall safety profile. • To assess preliminary evidence of anti-tumor activity of single agent talazoparib.	Not applicable.	Safety: • Adverse Events as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), timing, seriousness, and relationship to talazoparib. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 4.03), and timing. • Vital signs and ECG. • Concomitant medication use. Efficacy: • Unconfirmed ORR. • DOR.

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 1 study to evaluate the PK and safety of single agent talazoparib 1 mg QD in Chinese adult participants with advanced solid tumors who are resistant to standard therapy or for whom no standard therapy is available.

Approximately 15 participants will be enrolled to obtain about 12 evaluable participants to support mCRPC and other future potential indications registration in China. A single dose of talazoparib 1 mg is administered on Day -9, then continuous dosing will begin from C1D1. Participants will be given talazoparib 1.0 mg orally once daily until disease progression, death, unacceptable toxicity or withdrawal of consent. Dose modifications and reductions for talazoparib are to occur according to the Section 6.6.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study treatment will be given once daily in 28-day cycles. To understand the single-dose safety and single-dose PK assessments of talazoparib, a lead-in period preceding the continuous daily doses will be included. In the 9-day lead-in period, a single lead-in dose will be given on Day -9 and PK samples will be collected at pre-dose and 0.50, 1, 2, 4, 8, 24, 48, 96, 168 and 216 hours post dose. No talazoparib will be administered during the interval between the lead-in single dose and Day 1 of the first cycle. Additionally, to characterize the steady state PK profile, serial PK samples after multiple doses will be collected on Day 22 of the first cycle at pre-dose, 0.50, 1, 2, 4, 8, 24 hours post dose. Pre-dose samples will be collected on C1D21, C1D23.

Tumor assessments are to be done on D29 (±7 days window) and every 8 weeks (±7 days window) thereafter for the initial 12 cycles regardless of any dose interruptions or dose delays. After completion of Cycle 12 (at the beginning of Week 45), tumor assessment will be done per local standard practice. Tumor assessments should be repeated at the end of study visit if more than 6 weeks have passed since the last evaluation.

An End of Treatment visit will be performed for participants if the specified assessments are not completed in the last week (last 6 weeks for tumor assessments).

4.2. Scientific Rationale for Study Design

Talazoparib has a well-established safety, efficacy, and PK profile based on global clinical trial experience. As there was not clinical PK data with talazoparib in Chinese participants, the current Phase 1 study was initially designed to evaluate the PK profile of talazoparib as a single agent in Chinese participants with advanced solid tumors.

Clinical Pharmacology Consideration

The pharmacokinetics (PK) of talazoparib as a single agent was evaluated in participants with hematologic malignancies and solid tumors at doses of 0.025 to 2 mg QD administered orally, as a single dose and/or as multiple doses. The PK was similar in participants of each cancer type and no differences were apparent between males and females. Thus, unselected solid tumor patients are considered to be the target population of this study to support future potential registration of talazoparib in China.

As mentioned in Section 2.2.1, talazoparib was eliminated slowly with a mean $t_{½}$ of 89.8 hours based on absorption, distribution, metabolism, and excretion (ADME) study MDV3800-03. It should be noted that the $t_{½}$ value obtained from Study PRP-001 (62.4 hours) and Japan C3441030 study (50.73 hours) might be underestimated as the PK sampling time was only up to 168 hours versus 504 hours in Study MDV3800-03, thus to

fully characterize the single dose PK profile of talazoparib administration in Chinese solid tumor patients, 9 days (216 hours) sampling duration is proposed to characterize related PK parameter as precise as possible while considering solid tumor patients overall benefit/risk assessment.

Specifically, patients are required to be fasted for at least 8 hours prior to dosing and continue to be fasted 2 hours after dosing to control the variability due to food effect on C_{max}. Similarly, co-med with P-gp inhibitor and inducer are prohibited for Cycle 1 when intensive PK is scheduled after both single dose and multiple dose talazoparib administration to minimize the DDI effect to talazoparib exposure and potential alteration to efficacy. Notably, only potent P-gp inhibitor are prohibited to accommodate more co-med options for solid tumor patient as only sparse PK is schedule for post Cycle 1 PK assessment.

Study population consideration

Several Phase 1 Sponsor-initiated studies of talazoparib in solid tumor have been conducted globally. The first-in-human study (Study PRP-001 [C3441007]) in participants with advanced or recurrent solid tumors, a total of 110 participants were treated at a range of talazoparib doses (0.025-1.1 mg QD). Data from this study demonstrated objective responses and/or clinical benefit in participants with breast, ovarian/peritoneal, and pancreatic cancer; small-cell lung cancer (SCLC); and Ewing sarcoma. C3441030 study is an ongoing, Phase 1, open-label, dose escalation study is evaluating the safety, tolerability, PK and anti-tumor activity of talazoparib (0.75 mg and/or 1.0 mg QD) in Japanese patients with advanced solid tumors. As of the data cutoff date of 30 September 2019, efficacy data for this study was not available. In order to keep this study in historical context, PRP-001 and C3441030 study were reviewed and key features were incorporated. Chinese locally advanced or metastatic solid tumor **that is resistant to standard therapy or for which no standard therapy is available** will be enrolled in this study.

The results of PK analysis indicated that talazoparib CL/F was reduced in patients with renal impairment. Per talazoparib IB (Dec 2019), the recommended dose of talazoparib for patients with moderate renal impairment (30 mL/min ≤ CLcr <60 mL/min) should be reduced to 0.75 mg QD. No dose adjustment is recommended for patients with mild renal impairment (60 mL/min ≤ CLcr <90 mL/min). In C3441049 study, participants with calculated creatinine clearance <60 mL/min should be excluded as the starting dose is 1 mg QD.

Contraception consideration

There are no data from the use of talazoparib in pregnant women. Studies in animals have shown embryo-fetal toxicity and talazoparib was clastogenic in in vitro and in in vivo assays. Talazoparib may cause fetal harm when administered to a pregnant woman.

Talazoparib should not be given to pregnant participants or those who plan to become pregnant during treatment. Women of childbearing potential should be advised to avoid becoming pregnant while receiving talazoparib. Talazoparib may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus.

A highly effective method of contraception is required for female participants during treatment with talazoparib, and for at least 7 months after completing therapy. Advise male participants with female partners of reproductive potential and pregnant partners to use a condom (even after vasectomy), during treatment with talazoparib and for at least 4 months after the final dose (see Appendix 4).

4.3. Justification for Dose

In the first-in-human Phase 1 study (PRP-001, C3441007), the MTD and recommended Phase 2 dose (RP2D) for talazoparib as a single-agent was investigated using dose escalation scheme starting from 0.025 mg QD up to 1.1 mg QD. Two of 6 patients in Part 1 experienced a DLT (thrombocytopenia) at talazoparib 1.1 mg/day; therefore, 1.0 mg/day was considered the MTD and recommended Phase 2 dose. In global pivotal Phase 3 study 673-301 (EMBRACA, C34421009), 1 mg QD is given to the locally advance or metastatic breast cancer participants, which has been approved by US Food and Drug Administration (FDA), EU EMA and multiple other global health authorities.

In addition, Japan conducted a Phase 1 study (C3441030) to evaluate the safety, tolerability, preliminary efficacy, and PK profile of talazoparib as a single agent in Japanese participants with advanced solid tumors. The dose was escalated to the next dose level (1 mg QD) according to the pre-defined dose escalation scheme and based on the incidence of Dose limiting toxicities (DLTs) at the initial dose level (0.75 mg QD). As of 24 January 2019, a total of 9 participants were enrolled in the dose escalation part of the C3441030 study. DLT were not reported in any participants receiving 0.75 mg QD (n=3) or 1 mg QD (n=6). Therefore, the RP2D of single-agent talazoparib was determined to be 1 mg QD in Japanese participants with advanced solid tumors. Overall the safety profile in the dose escalation part was similar to the adverse events (AEs) observed in global studies of talazoparib. Most common AEs of single-agent talazoparib in Japanese participants were hematological toxicities and hepatotoxicities. Based on the preliminary PK analysis results (n=3 each in 0.75 mg QD and 1 mg QD), the PK profile of single-agent talazoparib in Japanese participants was comparable with that in Western population. These data also supported RP2D in Japanese participants.

A bridging study evaluation (BSE) consists of a summary and analysis of the efficacy, safety, and PK data that support the use of talazoparib 1 mg taken orally QD for the treatment of adult patients in Asian countries with gBRCA-mutated human epidermal HER2-negative locally advanced or metastatic breast. Conclusions from the data in this BSE shown that talazoparib exhibited similar PK in Asian Patients compared to non-Asian Patients. While population PK analysis showed that talazoparib exposure was 19.2% lower in Asian Patients compared with non-Asian Patients, this effect was not considered clinically relevant given that a) the within-subject talazoparib pre dose plasma concentration (C_{trough})in Asian Patients

are within the range of those in non-Asian Patients and b) the relatively small magnitude of lower average exposure in Asian Patients.

Based on the safety data of talazoparib and prior clinical experience as described above, talazoparib will be administered orally daily at 1 mg with provision for dose modifications as described in Section 6.6 in this protocol.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

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, is 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 age ≥18 years, inclusive, at Visit 1 (Screen 1).

    - Male participants are eligible to participate if they agree to the requirements described in protocol Section 10.4.1 during the intervention period and for at least 4 months after the last dose of study intervention.

    - A female participant is eligible to participate if she is not pregnant or breastfeeding. Women of childbearing potential (See details in protocol Section 10.4.2) must be willing to use a contraceptive method that is highly effective (as described in protocol Section 10.4.4) during the intervention period and for at least 7 months after the last dose of study intervention.

Type of Participant and Disease Characteristics:

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

3. Histological or cytological diagnosis of locally advanced or metastatic solid tumor that is resistant to standard therapy or for which no standard therapy is available.

4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

5. Adequate bone marrow function, including:

   - ANC ≥1,500/mm^3 or ≥1.5×10^9/L without the use of growth factor within 14 days before obtaining the hematology laboratory tests;

   - Platelets ≥100,000/mm^3 or ≥100×10^9/L without the use of platelet transfusions or growth factors within 14 days before obtaining the hematology laboratory tests;

   - Hemoglobin ≥9 g/dL, with last transfusion at least 14 days prior to the hematology laboratory tests.

6. Adequate renal function.

   - Estimated creatinine clearance (CLcr) ≥60 mL/min as calculated using the Cockcroft-Gault Formula (See Appendix 10).

7. Adequate Liver Function, including:

   - Serum TBili ≤1.5×ULN unless the patient has documented Gilbert syndrome (≤3×ULN for Gilbert syndrome);

   - AST and ALT ≤2.5×ULN (≤5.0×ULN if there is liver involvement by the tumor);

   - Alkaline phosphatase ≤2.5×ULN (≤5×ULN in case of bone metastasis).

8. Able to take oral medications.

9. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1, except for AEs not constituting a safety risk by investigator judgment.

10. Anticipate life expectancy ≥12 weeks.

Informed Consent:

11. 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. Participants with brain metastases.

2. Previous high-dose chemotherapy requiring stem cell rescue.

3. Myocardial infarction within 6 months before starting therapy, symptomatic congestive heart failure (New York Heart Association class III or IV), unstable angina, or unstable cardiac arrhythmia requiring medication. Stable cardiac arrhythmia (eg, chronic atrial fibrillation controlled by medication) can be eligible.

4. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

5. Known or suspected hypersensitivity to active ingredient/excipients.

6. 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:

7. Major surgery within 4 weeks prior to the first dose of study treatment.

8. Radiation therapy within 4 weeks prior to the first dose of study treatment. Palliative radiotherapy for the treatment of painful bony lesions within 2 weeks prior to the first dose of study treatment.

9. Any anti-tumor systemic cytotoxic therapies within 4 weeks prior to the first dose of study treatment (6 weeks for nitrosoureas or mitomycin-C), treatment with immune modulators (including, but not limited to, corticosteroids (at a prednisone-equivalent dose of >10 mg/day), cyclosporine and tacrolimus; locally active treatments such as Beconase are allowed) within 4 weeks prior to the first dose of study treatment.

10. Prior irradiation to >25% of the bone marrow (see protocol Appendix 9 Bone Marrow Reserve in Adults).

11. Current or anticipated use of P-gp inhibitor and/or inducer within 7 days prior to study intervention from lead-in to end of Cycle 1; concomitant use of potent P-gp inhibitor after Cycle 1 until the end of treatment. For a list of P-gp inhibitors and inducers, refer to protocol Section 6.5.

12. Prior treatment with a PARP inhibitor.

Prior/Concurrent Clinical Study Experience:

13. Participation in other studies involving investigational drug(s) within 4 weeks prior to the first dose of study treatment.

Diagnostic Assessments:

14. Active and clinically significant bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

Other Exclusions:

15. 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.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after discussion with the Sponsor's medical monitor.

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.

6.1. Study Intervention(s) Administered

Intervention Name	Talazoparib
Type	Intervention Type: Drug
Dose Formulation	Capsules
Unit Dose Strength(s)	1 mg; 0.25 mg 1 mg capsule will also be supplied as a starting dose; 0.25 mg capsule should only be used for participants who require dose reduction.
Dosage Level(s)	1 mg QD
Route of Administration	Oral
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.
[Current/Former Name(s) or Alias(es)]	Current Names: Talazoparib (PF-06944076) Former Name or Alias: MDV3800 or BMN 673

6.1.1. Administration

Talazoparib will be administered on a continuous basis. In the food effect study 673-103, food intake (a high-fat, high-calorie meal) had no impact on the AUC_{inf} while reduced the C_{max} by 46%. Consistent with findings from the food effect study, population PK analysis using data from Studies 673-301, 673-201, PRP-001, and PRP-002 showed food intake decreased absorption rate but had no impact on the extent of the absorption. To reduce the variability in C_{max} to better characterize the PK profile in Chinese after both single-dose and multiple dose, before serial PK sampling (Cycle 1 Day -9, Cycle 1 Day 22), talazoparib will be administered with approximately 240 ml water on an empty stomach ie, participants should refrain from food and beverages (except for water)should keep fasted for approximately 8 hours predose and 2 hour postdose. For the rest of PK sampling point, talazoparib may be taken with or without food.

A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 28 days.

Participants will swallow the talazoparib whole, and will not manipulate or chew the talazoparib capsule prior to swallowing. Talazoparib should be taken orally once daily (ie, continuous daily dosing) at approximately the same time each day (preferably in the morning). If a patient misses a day of treatment or vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of talazoparib (see details in Section 8.4).

On days of clinic visits, talazoparib should be taken at the clinic after completion of pre-dose sampling and assessments; on these PK sample dates, the clinic visit should be scheduled for approximately the same time of day that the dose is typically taken.

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. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. 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.

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

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

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

8. 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

A qualified staff member will dispense the study intervention using the IRT system via unique container numbers in the bottles provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant should be instructed to maintain the product in the bottle provided throughout the course of dosing and return the bottle to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). 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 dispensable unit (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.

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.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of talazoparib and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering talazoparib.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned capsules during the site visits and documented in the source documents and CRF. A patient diary will be provided to the participants to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient to include missed or changed talazoparib doses. The patient diary may also be used to support this part of the talazoparib accountability process. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of talazoparib capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF. Participants will be considered out of compliance if ≥20% of required doses are missed.

6.5. Concomitant Therapy

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

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions received by participants from 28 days before first dose until 28 days after the last dose will be recorded on the CRF.

6.5.1. P-gp Inhibitors and Inducers

Data from Study C3441004 indicated that coadministration of multiple daily doses of potent P-gp inhibitor itraconazole 100 mg twice daily with a single 0.5 mg talazoparib dose increased talazoparib total exposure (AUC_{inf}) and peak concentration (C_{max}) by approximately 56% and 40%, respectively, relative to a single 0.5 mg talazoparib dose administered alone; coadministration of multiple daily doses of a strong P-gp inducer, rifampin 600 mg, with a single 1 mg talazoparib dose, increased talazoparib C_{max} by approximately 37% whereas AUC_{inf} was not affected relative to a single dose of talazoparib 1 mg administered alone.

Considering the purpose and endpoint of this study, guidelines for concomitant use of talazoparib with P-gp inhibitors and inducers are as follows:

<u>7 days prior to lead-in to end of Cycle 1:</u>

To adequately evaluate the PK of talazoparib, P-gp inhibitors that result in ≥50% increase in the exposure of an in vivo probe P-gp substrate according to the 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/) should not be allowed: amiodarone, azithromycin, carvedilol, clarithromycin, cobicistat, curcumin, diosmin, dronedarone, erythromycin, flibanserin, fluvoxamine, glecaprevir/pibrentasvir, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, osimertinib, piperine, propafenone, quercetin, quinidine, ranolazine, ritonavir, saquinavir, sofosbuvir/velpatasvir/voxilaprevir, telaprevir, tipranavir, valspodar, vemurafenib, and verapamil.

Similarly, P-gp inducers that result in ≥20% reduction in the exposure of an in vivo probe P-gp substrate according to the 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/) should not be allowed: apalutamide, avasimibe, carbamazepine, danshen (salvia miltiorrhiza), efavirenz, phenytoin, rifabutin, rifampin, ritonavir, St. John's wort extract and tivantinib.

Beyond Cycle 1 onwards:

Potent P-gp inhibitors that result in ≥2-fold increase in the exposure of an in vivo probe P-gp substrate according to the 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/) should not be allowed: 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.

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 talazoparib may be needed.

Caution and monitoring for potential increased adverse reactions should be used upon concomitant use of the following transporter inhibitors with talazoparib throughout the study course: atorvastatin, azithromycin, conivaptan, curcumin, cyclosporine, diltiazem, diosmin, eliglustat, elacridar [GF120918], eltrombopag, felodipine, flibanserin, fluvoxamine, osimertinib, piperine, quercetin, schisandra chinensis extract and vemurafenib.

The list of potent P-gp inhibitors and transporter inhibitors to be used with caution will be updated annually and reflected in the Investigator Brochure.

6.5.2. Supportive Care

Supportive medications may be provided at the investigator's discretion. Hematopoietic growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Primary prophylactic use of granulocyte colony stimulating factors is not permitted but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guideline.[7] If neutropenic complications are observed in a cycle in which primary prophylaxis with colony stimulating factors (CSFs) was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered a reasonable alternative.

Allowed medications include (but are not limited to) anti-emetics, such as dexamethasone, metoclopramide, ondansetron, or aprepitant; anti-diarrheals, such as loperamide hydrochloride; and appetite stimulants such as megestrol acetate. Participants are not permitted to initiate treatment with bisphosphonates or denosumab during the study, but are permitted to continue on either of these treatments at the same dose as at randomization.

6.5.3. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. The concurrent use of herbal medicines with anti-cancer indication is not permitted.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions provided that the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression, after discussion with the Sponsor's medical monitor.

6.5.4. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and talazoparib required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping talazoparib is recommended at least 10 days prior to surgery. Postoperatively, the decision to reinitiate talazoparib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery. Surgical resection of target/non-target lesion is prohibited throughout the study period.

6.6. Dose Modification

Daily dosing of talazoparib can be interrupted for recovery from toxicity for up to 28 days. For interruptions longer than 28 days, treatment at the same or a reduced dose can be considered based on a discussion between the Sponsor or designee and Investigator if evidence of response or clinical benefit to talazoparib is noted.

Dose modifications should be made based on the observed toxicity, as summarized in Table 1 and Table 2.

Table 1. Dose Modification of Talazoparib Due to Adverse Events

Toxicity	Management of Adverse Events
Grade 1 or 2	No requirement for dose interruption or dose reduction. If the toxicity persists at Grade 2 (for ≥7 days), a dose reduction to the next lower dose level (eg, from 1 mg QD to 0.75 mg QD) may be implemented at the discretion of the Investigator.
Grade 3 or 4 Anemia (hemoglobin <8.0 g/dL)	Hold Talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9 g/dL or better, then resume talazoparib at a reduced dose. • If anemia with hgb <8.0 g/dL recurs after dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL then resume talazoparib at a further reduced dose. • If anemia persists for >4 weeks without recovery of hemoglobin to at least 9.0 g/dL despite supportive care measures at any dose level, discontinue talazoparib and consider referral to a hematologist. Transfusions and other supportive measures are permitted to support management of hematological toxicities at any occurrence.
Grade 3 or 4 Neutropenia (ANC <1000/μL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/μL, then resume talazoparib at a reduced dose. If neutropenia recurs after the dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/μL, then resume talazoparib at a further reduced dose. If neutropenia persists for >4 weeks without recovery to ≥1500/μL at any dose level despite supportive care measures, discontinue talazoparib and consider a referral to a hematologist. G-CSF and GM-CSF may be used at investigators discretion for the supportive treatment of neutropenia at any occurence.
Grade 3 or 4 Thrombocytopenia (platelets <50,000/μL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥50,000/μL, then then resume talazoparib at a reduced dose. If thrombocytopenia (<50,000/μL) recurs after one dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥75,000/μL, then resume talazoparib at a further reduced dose. If thrombocytopenia persists for >4 weeks without recovery to ≥50,000/μL despite supportive care measures, discontinue talazoparib and consider a referral to a hematologist. Thrombopoietin analogues and/or platelet transfusions may be used at investigators discretion for the supportive treatment of thrombocytopenia at any occurrence.
Nonhematologic laboratory Grade ≥3 events determined	Hold talazoparib as follows: • For Grade 3 laboratory abnormalities, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade

Table 1. Dose Modification of Talazoparib Due to Adverse Events

Toxicity	Management of Adverse Events
to be clinically significant, except abnormal liver tests	for creatinine increases). Resume talazoparib at the same dose or reduce to one dose level. • If Grade 3 laboratory abnormality recurs, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Reduce talazoparib one dose level. • For Grade 4 laboratory abnormalities, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Reduce talazoparib one dose level. • Talazoparib must be discontinued if a Grade 4 adverse event recurs after treatment resumes. 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 14 days or for Grade 4 toxicity lasting longer than 3 days. Talazoparib may be resumed at a reduced dose level if clear clinical benefit is observed, after discussion with the Sponsor.
Grade ≥3 abnormal liver tests	Subjects who develop abnormal liver tests ([AST, ALT, total bilirubin [TBili]), signs or symptoms consistent with hepatitis during study treatment may meet the criteria for temporarily withholding or permanently discontinuing study drug talazoparib. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities if any of the following occur: • Subjects who develop AST or ALT >5 x ULN (AST/ALT >8 × ULN for subjects with hepatic involvement) without TBili >2 x ULN; OR • Subjects with baseline total bilirubin <1.5 x ULN who subsequently present with >3 x ULN; OR • Subjects with baseline total bilirubin >1.5 x ULN and <3 x ULN (eg, Gilberts) who subsequently present with bilirubin >5 x ULN. If abnormalities resolve to baseline values within 2 weeks, there are no signs of DILI, and none of the permanent discontinuation criteria are met, then upon discussion with the Sponsor, the investigator may re-challenge at a reduced dose level. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities if any of the following occur: • Subjects who develop with AST OR ALT values >3 × ULN (AST/ALT >8 × ULN for subjects with hepatic involvement) AND a Tbili value >2 × ULN. • Subjects with AST/ALT >5 × ULN that persists for more than 7 days (AST/ALT >8 × ULN for subjects with hepatic involvement).

Table 1. Dose Modification of Talazoparib Due to Adverse Events

Toxicity	Management of Adverse Events
	• Subjects with AST/ALT >20 × ULN that persists for longer than 3 days. Subjects with Tbili >3 × ULN that persists for longer than 7 days (>5 × ULN for subjects with Gilbert's disease). Guidelines for follow-up for possible drug-induced liver injury after the liver test abnormalities resolve to baseline grade are provided in Section 10.5.
Nonlaboratory Grade ≥3 events	Hold talazoparib as follows: For Grade 3 adverse events, hold talazoparib until the adverse event resolves to Grade ≤1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level. For Grade 4 adverse events, hold talazoparib until the adverse event resolves to Grade <1 or baseline. Resume talazoparib at a reduced dose level.

Refer to Table 2 for additional information. Dose reduction of talazoparib by 1 and, if needed, 2 dose levels (Table 1) will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 3 dose reductions will be discontinued from the treatment and entered into the follow-up phase, unless otherwise agreed between the investigator and the sponsor. All dose modifications/adjustments must be clearly documented in the patient's source notes and case report form (CRF).

Table 2. Dose Modifications for Toxicities

	Dose Level
Initial dose level	1 mg QD
First dose level reduction	0.75 mg QD
Second dose level reduction	0.5 mg QD
Third dose level reduction	0.25 mg QD

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants after the end of the study.

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 list reasons for discontinuation of study intervention.

- Pregnancy (see follow up requirement in Section 8.3.5.1);
- Unacceptable toxicity (see details in Table 1);
- Disease-State Criteria (eg, objective disease progression; global deterioration of health status requiring discontinuation);
- Death;
- Patient refused further treatment;
- Study terminated by sponsor;
- Lost to follow-up;
- Significant protocol deviation.

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 at least 28 calendar days after last dose of talazoparib. 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, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Temporary Discontinuation

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator. Criteria required before treatment can resume are described in the Section 6.6.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle. If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Section 6.6, unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

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.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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 also 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 study intervention 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 or not 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.

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, blood chemistry and imaging) 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.

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 well-being 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.

The total blood sampling volume for individual participants in this study will depend upon the actual duration of treatment. 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.

Volume of blood collected for each test refer to Table 3.

Table 3. Blood Sampling Volume for Each Test

Testing	Blood sampling volume
Hematology	3 mL
Chemistry	5 mL
HCV, HBV test	5 mL
HIV test	5 mL
PK	3 mL
Pregnancy (blood)	3 mL
FSH	3 mL

The actual blood sampling volume may be less, please refer to the site operational manual.

8.1. Efficacy Assessments

Tumor assessment will be conducted in this study to explore the preliminary efficacy profile of talazoparib monotherapy in Chinese Participants with advanced solid tumor.

8.1.1. Imaging Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

A brain MRI or CT is to be performed at screening/baseline to evaluate participants for presence/absence of brain metastases. Bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. CT or MRI scans to be done on D29 (±7 days window) and every 8 weeks (±7 days window) thereafter for the initial 12 cycles regardless of any dose interruptions or dose delays.

CT or MRI scans to be done on D29 (±7 days window) and every 8 weeks (±7 days window) thereafter for the initial 12 cycles regardless of any dose interruptions or dose delays. After completion of Cycle 12 (at the beginning of Week 45), tumor assessment will be done per local standard practice. Tumor assessments should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation.

Given the exploratory nature of the efficacy endpoint, confirmation of response (complete response [CR]/partial response [PR]) is not required. As clinically indicated, CT/MRI will be repeated by investigator's discretion.

Assessment for anti-tumor activity

Anti-tumor activity will be assessed through radiological tumor assessments conducted as specified in the SoA. Assessment of response will be made using RECIST version 1.1 (see Section 10.7).

8.2. Safety Assessments

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 general appearance, head, oropharynx, eyes, ears, nose, neck, thyroid, lung, heart, breast, abdomen, musculoskeletal, skin. Height and weight will also be measured and recorded. Height will be recorded at screening only. Weight will be measured according to the SoA.

A brief physical examination will be focused on physical examinations at the discretion of the investigator based on the patient's clinical condition. At a minimum, assessments of the skin, lungs, heart, and abdomen (liver and spleen).

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

8.2.2. Vital Signs

Temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure will be assessed.

Blood pressure and pulse rate measurements will be assessed in the sitting position after the participant has been resting quietly for at least 5 minutes and prior to dosing on dosing days with a completely automated device. Manual techniques will be used only if an automated device is not available.

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, RR, QT intervals, QTc, QTcF 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.

If a) a postdose QTc interval remains ≥60 msec from the baseline **and** is >450 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 6.

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 significantly abnormal during participation in the study or within 28 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 5 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 study intervention. 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/legally authorized representative 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 study intervention), 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.

MDS, AML and second primary malignancies are adverse events of special interest in this study. Any diagnosis of MDS, AML or second primary malignancies for any participant enrolled will be reported as an SAE.

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 follow-up (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 an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 study intervention.
- A male participant who is receiving or has discontinued study intervention 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 study intervention 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 study intervention by ingestion, inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, 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 in female participants after the start of study intervention and until 7 months after the last dose. And female partners of male participants will be collected after the start of study intervention and until 4 months after the last dose.

- 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), 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

An exposure during breastfeeding occurs if:

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (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 study intervention 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 study intervention, 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

Death events should be reported as SAEs if meet the criteria.

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

The following DREs are common in participants with condition under study and can be serious/life threatening:

- Non-fatal progression of the malignancy under study (including signs and symptoms of progression).

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the efficacy CRF page in the participant's CRF within the appropriate time frame.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML), and second primary malignancies are the AEs of special interest in this study.

- MDS/AML

Complete blood counts should be obtained at baseline and monitored for signs of hematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued. Any diagnosis of myelodysplastic syndrome (MDS) or AML for any participant enrolled will be reported as an SAE.

MDS and AML, and second primary malignancies.

- Second primary malignancies

Due to talazoparib's mechanism of action, and demonstration of clastogenicity in pre-clinical studies, second primary malignancies are considered a potential risk for talazoparib. In the talazoparib 1 mg QD Population, 7 AEs of second primary malignancies were reported in 6 participants (squamous cell carcinoma of skin [2 participants], and basal cell carcinoma, glioblastoma multiforme, intraductal proliferative breast lesion, neoplasm skin, and ovarian neoplasm [1 participant each]. These second primary malignancies were mostly skin malignancies. In general, latency to diagnosis of the malignancy was relatively short, making a relationship with talazoparib unlikely, and in some cases, other risk factors were reported. None of the events were considered related to talazoparib by the investigator.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.9. Medication Errors

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

Exposures to the study intervention 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;
- 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 protocol-specified dose of 1 mg within a day will be considered an overdose.

There is no specific treatment in the event of talazoparib overdose, and symptoms of overdose are not established.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities 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 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

6. Treatment with talazoparib should be stopped, and physicians should consider gastric decontamination, follow general supportive measures and treat symptomatically.

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 3 mL, to provide a minimum of 1.5 mL, will be collected for measurement of plasma concentrations of talazoparib 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.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AEs. In case of QTc values >500 msec, a blood sample for PK analysis should be collected. The date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows. In the event of any dose interruption or reduction before Cycle 1

Day 22, the intensive PK sampling shall be postponed to Day 1 or 15 of next cycle but no later than Cycle 4 if consecutive 20 days dosing prior to PK sampling is achieved.

PK samples will be assayed for talazoparib using a validated analytical method in compliance with Pfizer standard operating procedures (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.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

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

Do not apply.

9.2. Sample Size Determination

To support registration of mCRPC and other future potential indications in China, 12 evaluable participants will be needed to characterize Chinese PK profile based on available talazoparib PK data globalwise and with the intention to satisfy regulatory requirement by China National Medical Products Administration (NMPA) in terms of PK evaluation in Chinese population. Considering non-evaluable participants, it is estimated that approximately 15 patients are needed.

9.3. Analysis Sets

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

Participant Analysis Set	Description
PK concentration population	Defined as all participants enrolled and treated who have at least 1 PK concentration in the single-dose and/or multiple-dose PK part.
PK parameter analysis population	Defined as all participants enrolled and treated who have at least 1 of the PK parameters of primary interest in the single-dose and/or multiple-dose PK part.
PK evaluable analysis set	Defined as all participants in the PK parameter analysis set who complete both the single dose PK and multiple dose PK parts without major protocol deviations.
Safety/Efficacy	Includes all enrolled participants who receive at least one dose of study medication.

9.4. Statistical Analyses

Pharmacokinetic parameters and plasma concentration data will be summarized as the primary analysis for this study. In addition, safety data including adverse events (AE), laboratory abnormalities and electrocardiogram measurements (ECG), as well as efficacy information reflected by objective response (OR) and duration of response (DOR) will also be summarized and estimated.

9.4.1. Primary Endpoint(s)

PK parameters of talazoparib following single dose administration will be derived from the concentration-time profiles as shown in the table below.

Parameter	Definition	Method of determination
C_{max}	Maximum plasma concentration	Observe directly from data
T_{max}	Time for C_{max}	Observe directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{τ}	Area under the plasma concentration versus time curve from time zero to the $time_{\tau}$	Linear/Log trapezoidal method
AUC_{inf}	Area under the plasma concentration versus time curve from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis; kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
CL/F	Apparent oral clearance	$Dose/AUC_{inf}$
V_z/F	Apparent volume of distribution	$Dose/(AUC_{inf} * k_{el})$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
$t_{1/2}$	Terminal plasma half-life	$Log_e(2)/k_{el}$

PK parameters of talazoparib following multiple dose administration will be derived from the concentration-time profiles as shown in the table below.

Parameter	Definition	Method of determination
C_{max}	Maximum plasma concentration	Observe directly from data
T_{max}	Time for C_{max}	Observe directly from data as time of first occurrence within τ at steady state
C_{min}	Minimum plasma concentration	Observe directly from data
AUC_{τ}	Area under the plasma concentration versus time curve within a dosing interval of τ (=24 hr)	Linear/Log trapezoidal method
CL/F	Apparent clearance	Dose/AUC_{τ}
R_{ac}	Observed accumulation ratio	$R_{ac}=AUC_{\tau}/AUC_{sd,\tau}$, where $AUC_{sd,\tau}$ is AUC_{24}
R_{ss}	Steady-state accumulation ratio	$R_{ss}=AUC_{\tau}/AUC_{inf}$, where AUC_{inf} is from single dose

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

Summary of pharmacokinetic parameters will be for PK parameter analysis set and PK evaluable analysis set. The PK parameters AUC_{10}, AUC_{24}, AUC_{last}, AUC_{inf}, C_{max}, T_{max}, CL/F, $t_{1/2}$, V_z/F and kel of talazoparib following single dose administration of talazoparib will be listed and summarized descriptively for Lead-in phase. The PK parameters AUC_{τ}, C_{max}, C_{min}, T_{max}, CL/F, V_z/F, $t_{1/2}$, R_{ac}, and R_{ss} of talazoparib following multiple dose oral administration of talazoparib will be listed and summarized descriptively.

The plasma concentration data for talazoparib will be listed and summarized descriptively by day and nominal PK sampling time for subjects in the PK concentration analysis set. Overlay multiple patient profiles of the plasma concentration-time data for talazoparib will be plotted using actual PK sampling time (separate plots for single and multiple dose PK). For mean and median plots of talazoparib plasma concentration-time, the nominal PK sampling time will be used. Mean and median profiles will be presented on both linear-linear and log-linear scales. For individual patient plots of talazoparib, the actual PK sampling time will be used, while the predose time will be set to zero.

The trough plasma concentration of talazoparib on Days 19-21 in Cycle 1 will also be plotted for visual inspection of steady-state condition.

9.4.2. Secondary Endpoint(s)

9.4.2.1. Safety

Safety analysis will be based on safety set that was defined in Section 9.3.

Adverse events and laboratory abnormalities

Adverse events (AEs) will be coded to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the National Cancer Institutes (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

The focus of AE summaries will be on Treatment-Emergent Adverse Events (TEAEs), those with initial onset after the first dose of study treatment.

An event will be considered treatment related if the investigator considered the event related to the study drug. The number and percentage of participants who experienced any AE, serious AE (SAE), treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs on the entire study period as well as by relatedness to study treatment.

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay based on the NCI CTCAE v4.03 severity grade. Shift tables will be provided to examine the distribution of laboratory toxicities. The analyses will summarize laboratory tests on the entire study period. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal or not done.

Electrocardiogram measurements

All ECGs obtained during the study will be evaluated for safety. The average of the triplicate ECG measurements will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

Changes from baseline will be defined as the change of QTc post dose from the average of the pre-dose triplicate values.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Bazett's, Fridericia's and possibly a study specific factor). Data will be summarized and listed for QT, HR, RR, PR, QRS and QTc by time. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment by day and time point. For each patient, the maximum change from baseline will be calculated as well as the maximum post-baseline value across time points. Categorical analysis of the QTc data will be conducted and summarized as follows:

The number of participants with maximum change from baseline in QTc (<30, 30-59, and ≥60 msec).

The number of participants with maximum post-dose (post-baseline) QTc (<450, 450-<480, 480-≤500, and >500 msec).

9.4.2.2. Efficacy

Objective response (OR)

Objective response by investigator assessment is defined as a complete response (CR) or partial response (PR) according to the RECIST version 1.1 recorded from Cycle 1 Day 1 (C1D1) until disease progression, start of subsequent anti-cancer therapy or death due to any cause.

A participant will be considered to have achieved an OR if the participant has a complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the participant will be considered a non-responder in the OR rate analysis. Additionally, participants with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis. If participants with non-measurable disease are enrolled, they are included in the aforementioned calculation of OR rate as well, however, a subgroup calculation of OR rate should be conducted among participants who are with measurable disease at baseline.

The OR rate (ORR) will be estimated by dividing the number of participants with objective response (CR or PR) by the number of participants in the safety analysis set (response rate). An exact 95% confidence interval (CI) by Clopper–Pearson will be provided for the ORR.

Duration of response (DOR)

For participants with an objective response (CR or PR), duration of response (DOR) is the time from first documentation of CR or PR to date of first documentation of objective progression or death. Date of first documentation of PD and date of first documentation of CR or PR will be based on investigator assessment of response. DOR data will be censored on the date of the last tumor assessment on study for participants who do not have objective tumor progression and who do not die due to any cause while on study. DOR will only be calculated for the subgroup of participants with an objective response.

DOR will be summarized in the efficacy analysis set using the Kaplan-Meier method and displayed graphically. Median event time and 95% confidence interval for the median will be provided.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

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 subinvestigators 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 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.

Participants who are rescreened are required to sign a new ICD.

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 form and are password protected 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 monitoring plan.

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 the clinical monitoring plan.

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 sponsor or designee/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

Publication will be addressed in the clinical study agreement.

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 the supporting study portal.

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 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Neutrophils % Eosinophils % Monocytes % Basophils % Lymphocytes %	BUN or urea Creatinine Glucose (fasting) Calcium Sodium Potassium Magnesium Chloride AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein CLcr[a]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase/leukocytes Urobilinogen Urine bilirubin Microscopy[b]	At screening only: • FSH[c] • Virus test (HBV, HCV, HIV)[d] For WOCBP only • Pregnancy test (beta human chorionic gonadotropin (β-hCG)[e]

a. Calculated with serum creatinine, age, weight collected at baseline.
b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase/leukocytes.
c. For confirmation of postmenopausal status only.
d. Perform within 28 days prior to first study treatment, including HBV (HBsAg and HBcAb), HCV antibody, and HIV antibody.
e. 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.

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 patient 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:

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

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.

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.
- 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 an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

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) ***plus*** an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below.
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- Male participants should be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak when having sexual intercourse with a WOCBP who is not currently pregnant.

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), preferably with low user dependency, 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). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, 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). In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. 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 <u>not</u> considered WOCBP:

1. Premenarchal.

2. 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.

3. 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.

Highly Effective Methods That Have Low User Dependency

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 WOCBP 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.

Highly Effective Methods That Are User Dependent

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

    - Oral;

    - Intravaginal;

    - Transdermal;

- Injectable.

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

   - Oral;

   - Injectable.

3. 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.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- 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).

10.5. Appendix 5: 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, the possibility of hepatic neoplasia (primary or secondary) should be considered.

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.

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That May 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 May 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.

10.7. Appendix 7: RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING LESION AT BASELINE

MEASURABLE LESIONS

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: THE SHORTEST AXIS IS USED AS THE DIAMETER FOR MALIGNANT LYMPH NODES, LONGEST AXIS FOR ALL OTHER MEASURABLE LESIONS.

NON-MEASURABLE DISEASE

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion patiented to other local treatment) is non-measurable unless it has progressed since completion of treatment.

NORMAL SITES

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

TARGET LESIONS

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce, the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: WHEN NODAL LESIONS DECREASE TO <10 MM (NORMAL), THE ACTUAL MEASUREMENT SHOULD STILL BE RECORDED.

NON-TARGET DISEASE

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made, the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

TARGET DISEASE

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): At least a 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

    - one or more target measurable lesions have not been assessed;

    - or assessment methods used were inconsistent with those used at baseline;

    - or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

- or one or more target lesions were excised or irradiated and have not reappeared or increased.

NON-TARGET DISEASE

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

NEW LESIONS

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

SUPPLEMENTAL INVESTIGATIONS

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

SUBJECTIVE PROGRESSION

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

The objective response status is to be determined by evaluation of target and non-target disease as shown in Table 5 and Table 6.

Table 5. Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 6. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study).

10.8. Appendix 8: ECOG Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am J Clin Oncol 5:649-655, 1982.

10.9. Appendix 9: Bone Marrow Reserve in Adults

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head :			136.6	13.1	**13.1**
	Cranium	165.8	0.75	124.3		
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle :			86.7	8.3	8.3
	2 Humerus, head & neck	26.5	0.75	20.0		
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs :			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	**10.2**
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	**36.2**
	2 os coxae	310.6	0.75	233.0	22.3	
FEMUR	2 Femoral head and neck	53.0	0.75	40.0	3.8	**3.8**

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
VERTEBRAE	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar) :			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		**1497.7**		**1045.7**	**100.0**	**100.0**

10.10. Appendix 10: Cockcroft-Gault Formula

CL_{cr}={((l40–age) x weight)/(72xS_{Cr})}x 0.85 (if female)

Abbreviations/ Units

CL_{Cr} (creatinine clearance) = mL/minute

Age = years

Weight = kg

SCr (serum creatinine) = mg/dL

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	absolute neutrophil count
ANOVA	Analysis of Variance
AST	aspartate aminotransferase
AUC	Area Under the Concentration-Time Curve
$AUC_{(0-24)}$	Area Under the Concentration-Time Curve From Time 0 to 24 Hours
AUC_{inf}	area under concentration-time curve from time 0 to infinity
AUC_{last}	Area under the plasma concentration versus time curve from time zero to the time of C_{last}
$AUC_{sd,inf}$	Area under the plasma concentration versus time curve from time zero to infinity at steady state
$AUC_{sd,\tau}$	Area under the plasma concentration versus time curve within a dosing interval of τ (=24 hr) at steady state
AUC_{τ}	Area under the plasma concentration versus time curve from time zero to the time τ
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BCRP	Breast Cancer Resistance Protein
BICR	blinded independent central review
bpm	beats per minute
BP	blood pressure
BRCA	Breast Cancer gene
BSA	bovine serum albumin
BSE	bridging study evaluation
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL_{cr}	creatinine clearance
CL/F	apparent oral clearance
C_{max}	maximum plasma concentration
C_{min}	Minimum Plasma Concentration

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CT	clinical trial
C_{trough}	pre dose plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-Drug Interaction
DILI	drug-induced liver injury
DOR	Duration of response
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRE	disease-related event
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
f_u	Fraction of Unbound
gBRCAm	germline BRCA-mutated
GCP	Good Clinical Practice
GI	Gastrointestinal
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
HIPAA	Health Insurance Portability and Accountability Act
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
IQR	interquartile range
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
IWR	interactive Web-based response
k_{el}	Constant of elimination rate
LFT	liver function test
mCRPC	metastatic castration resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MD	multiple dose
MDS	Myelodysplastic Syndrome
MRI	magnetic resonance imaging
MTD	Maximum Tolerated Dose
N/A	not applicable
NCI	National Cancer Institute
NIMP	noninvestigational medicinal product
NMPA	National Medical Products Administration
NMSC	nonmelanoma skin cancer
ORR	objective response rate
PARP	Poly(Adenosine Diphosphate-Ribose) Polymerase
PD	disease progression
PD-L1	programmed death ligand 1
PFS	progression-free survival
P-gp	P-Glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PS	Performance Status
PT	preferred term
PVC	premature ventricular contraction/complex
QD	Once Daily

Abbreviation	Term
ADME	absorption, distribution, metabolism, and excretion
OR	objective response
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
Rac	observed accumulation ratio
RBC	red blood cell
Rss	steady-state accumulation ratio
PCT	physician's choice treatment
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small-cell lung cancer
SCr	serum creatinine
SD	single dose
SD	stable disease
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
t1/2	Terminal Half-Life
TBili	total bilirubin
TEAEs	treatment-emergent adverse events
T_{max}	Time to Reach Maximum Plasma Concentration
ULN	upper limit of normal
US	United States
Vz/F	Apparent volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential
→	ongoing/continuous event

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