Pfizer, Inc.

CLINICAL RESEARCH PROTOCOL

Study Title:	A Single-Arm, Open-Label, Multicenter, Extended Treatment, Safety Study in Patients Treated With Talazoparib
Protocol Identifier:	MDV3800-13 (C3441010)
Phase:	2
Investigational Product:	Talazoparib (also known as MDV3800, BMN 673, PF-06944076)
Indication:	Advanced solid tumors (from multiple originating studies)
Sponsor:	Pfizer, Inc. 235 East 42nd St. New York, NY 10017 Telephone: +1 (212) 733-7900 Fax: +1 (415) 543-3411
Reference Numbers:	United States IND CCI EudraCT 2016-001972-31
Sponsor Medical Monitor:	PPD MD Telephone: PPD Mobile: PPD Email: PPD
Original Protocol:	v1.0 – 06 Jun 2016
Amendment 1:	v2.0 – 29 Jul 2016
Amendment 2:	v.3.0 – 15 May 2017 (Poland)
Amendment 3:	v4.0 – 24 Aug 2018
Amendment 4:	v5.0 – 14 Nov 2018 (Investigational sites US0002, US0117, US0121, US0839, US230)

This study will be conducted according to the principles of Good Clinical Practice as described in International Conference on Harmonisation guidelines, including the archiving of essential documents.

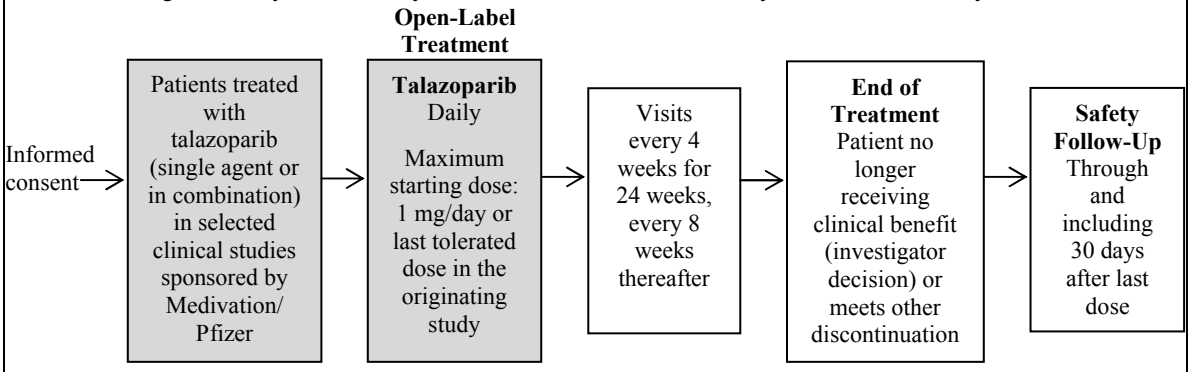
Confidentiality Statement

SYNOPSIS

Title of Study: A Single-Arm, Open-Label, Multicenter, Extended Treatment, Safety Study in Patients Treated With Talazoparib
Protocol Identifier: MDV3800-13 (C3441010)
Phase of Development: 2
Number of Patients: Approximately 150
Study Centers: Approximately 50 (international)
Study Objective: To obtain additional safety data on long-term talazoparib use
Methods: This is a single-arm, open-label, extended treatment, safety study in patients treated with talazoparib (also known as MDV3800, BMN 673, PF-06944076,) as a single agent or in combination with another agent in qualifying originating clinical studies sponsored by Medivation/Pfizer. The safety and tolerability of long-term talazoparib use will be evaluated, and the data collected will be limited to safety assessments. The study provides access to single-agent talazoparib for qualifying patients who may benefit from continuing therapy with talazoparib. Eligible patients must have received talazoparib in a qualifying study and have no ongoing grade 3 or 4 talazoparib-related toxicities. Patients must receive their first dose of talazoparib in this protocol within 2 months after their last dose of talazoparib in the originating study and may not receive any intervening antineoplastic therapies before starting this study. Patients will have clinic visits approximately every 4 weeks for the first 24 weeks and then approximately every 8 weeks thereafter (additional visits for laboratory testing every 2 weeks through week 9 and every 4 weeks thereafter) or as clinically indicated (patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study eg, if a PRP-001 patient is on an every 4 week schedule in the originating study, the patient is required to complete the week 5 and week 9 visits but not the Complete Blood Count (CBC) assessments at week 3 and week 7; afterwards, these patients would follow the schedule of activities in Appendix 1). Additional clinic visits and laboratory testing may be necessary to monitor safety (eg, for dose modification, hematologic toxicity, pregnancy testing). The maximum starting dose of talazoparib will be 1 mg/day or the last tolerated dose administered in the originating study. Talazoparib capsules will be administered by mouth once daily with or without food at approximately the same time of day. Patients receiving talazoparib as combination treatment in the originating study will receive talazoparib as a single agent in this extended treatment study. Talazoparib administration may continue as long as the investigator considers treatment to be providing clinical benefit or until other study discontinuation criteria are met (Section 5.3). The addition of any other antineoplastic therapy and the concurrent use of investigational agents during the study are prohibited. Study assessments will include adverse events, local clinical laboratory tests, concomitant medications, physical examinations, and vital signs (and weight). Clinical laboratory tests (hematology, serum chemistry) will be performed every 4 weeks through week 25 and every 8 weeks thereafter during the study. Complete blood count (CBC) tests will be completed every 2 weeks through week 9 and every 4 weeks thereafter. Women of childbearing potential must have a pregnancy test every 4 weeks. Safety follow-up will be through and including 30 days after the last dose of talazoparib.

Study Schematic:

Key assessments: laboratory tests, physical examinations, adverse events.
Patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study.



Key Eligibility Criteria:
Eligible patients must have received talazoparib as a single agent or in combination with another agent in a qualifying Medivation/Pfizer-sponsored study in advanced solid tumors and have no ongoing National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 talazoparib-related toxicities. All patients must provide signed informed consent. Eastern Cooperative Oncology Group (ECOG) must be ≤2. Patients must have tolerated ≥0.25 mg/day talazoparib during the originating study. Women of childbearing potential must have a negative pregnancy test before entering the study, be willing to have additional pregnancy tests while receiving talazoparib, and agree to avoid pregnancy by using a highly effective birth control method from the first dose of talazoparib through 7 months after the last dose. Male patients must use a condom when having sex with a pregnant woman or with a woman of childbearing potential from the first dose of talazoparib through 4 months after the last dose. Patients who permanently discontinued from any Medivation/Pfizer-sponsored study with talazoparib alone or in combination with another agent or who received an antineoplastic therapy after treatment with talazoparib in the originating study are excluded.

Test Product, Dose, and Mode of Administration:
Talazoparib is provided as the 4-methylbenzenesulfonate (tosylate) salt and has the chemical name (8S,9R) 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1H-1,2,4-triazol-5-yl)-3H-pyrido[4,3,2-de]phthalazin-3-one.
The drug product is a capsule containing talazoparib tosylate and silicified microcrystalline cellulose. The capsules for each dose strength will be provided in dose-specific colors.
Talazoparib (maximum starting dose of 1 mg/day or last tolerated dose administered in the originating study) will be self-administered orally once daily at approximately the same time each day. Talazoparib will be swallowed whole with a glass of water and may be taken with or without food.

Reference Therapy, Dose, and Mode of Administration:
Not applicable.

Duration of Treatment (End of Study):
Patients will continue receiving talazoparib as long as the investigator considers treatment to be providing clinical benefit or until other study discontinuation criteria (Section 5.3) are met.
The study may continue until the last patient has stopped deriving clinical benefit as assessed by the investigator or until the last patient meets other study discontinuation criteria (anticipated to be approximately 4 years).

Statistical Methods:
All safety analyses will be conducted using the safety population defined as all patients who receive any amount of talazoparib.
Safety will be evaluated using summaries of adverse events, vital signs, and clinical laboratory tests. Treatment-emergent safety data will be collected from the first dose of talazoparib through through and including 30 days after the last dose. Drug exposure will be summarized using descriptive statistics.
All adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using CTCAE. The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, severity, seriousness, and outcome (eg, leading to permanent treatment discontinuation). Descriptive statistics will be used.
Laboratory values will be classified for severity using the CTCAE. Laboratory shift tables of baseline results versus postbaseline results will be produced as appropriate.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BRCA	Breast cancer susceptibility gene
CBC	Complete blood count
CFR	Code of Federal Regulations
CL/F	Apparent oral clearance
Cmax	Maximum plasma concentration
Cmin	Plasma trough concentration
CR	Complete response
CRF	Case Report Form
CSA	Clinical study agreement
CT	Clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
EC	Ethics committee (global term including institutional
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure during pregnancy
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation
ID	Identification
IP	Investigational product
INR	International normalized ratio
IRT	Interactive Response Technology
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NASH	Nonalcoholic fatty liver disease
PARP	Poly(ADP-ribose) polymerase
P-gp	P-glycoprotein
PK	Pharmacokinetics
PR	Partial response
SAE	Serious adverse event
SRSD	Single reference safety document
TBili	Total bilirubin
ULN	Upper limit of normal
US	United States

1. INTRODUCTION

MDV3800-13 is designed to evaluate the safety and tolerability of long-term talazoparib use for patients who were treated with talazoparib as a single agent or in combination with another agent in a qualifying talazoparib clinical study who may benefit from continuing therapy with talazoparib.

1.1. Background

Talazoparib (also known as MDV3800, BMN 673, PF-06944076) is a potent, orally bioavailable, small molecule poly(ADP-ribose) polymerase (PARP) inhibitor in development for the treatment of a variety of human cancers. PARP inhibitors including talazoparib exert cytotoxic effects via 2 mechanisms, inhibition of PARP1 and PARP2 catalytic activity, and PARP trapping, a process in which PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, preventing DNA repair, replication, and transcription (Murai et al, 2012).[5] Inhibition of PARP catalytic activity contributes to the process of synthetic lethality, as it results in persistent single-strand breaks that require homologous recombination DNA repair for survival. Stabilized PARP-DNA complexes (ie, trapped) inhibit DNA repair, replication, and transcription, and are more cytotoxic than unrepaired single-strand breaks because they do not readily dissociate. Although other PARP inhibitors possess both activities, in vitro studies demonstrated that talazoparib has greater PARP trapping activity than other PARP inhibitors in clinical development (Hopkins et al, 2015; Murai et al, 2014).[3,6]

1.2. Summary of Relevant Clinical Experience With Talazoparib

Approximately 319 patients have received talazoparib in company-sponsored studies as of 30 Nov 2015, including 3 studies in solid tumors and 1 in hematologic malignancies. Studies include a phase 1 study (PRP-001) in advanced solid tumors, a phase 2 study (673-201) in locally advanced and/or metastatic breast cancer, and a phase 3 study (673-301) in locally advanced and/or metastatic breast cancer.

1.2.1. Efficacy

PRP-001 is a phase 1, open-label, safety, pharmacokinetic (PK), and dose-escalation (0.025-1.1 mg/day) and expansion (1 mg/day) study of talazoparib monotherapy in 110 patients with advanced or recurrent solid tumors with DNA repair deficiencies. As of the data cutoff date of 30 Nov 2015, objective responses (complete response [CR] or partial response [PR]) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) were observed in 8 of 18 patients (44%) with breast cancer and 12 of 25 patients (48%) with ovarian/primary peritoneal cancer with deleterious germline breast cancer susceptibility gene (BRCA) mutations; clinical benefit (CR, PR, or stable disease ≥24 weeks) was observed in 13 of 18 patients (72%) and 19 of 25 patients (76%), respectively. Seven of 12 patients with confirmed objective responses were treated with talazoparib at 0.1 to 0.9 mg/day, and 5 patients were treated at the recommended dose of 1 mg/day.

Additional information on the clinical efficacy of talazoparib is provided in the talazoparib investigator brochure.

1.2.2. Safety

The safety of talazoparib as monotherapy is based on phase 1 and 2 studies in patients with advanced cancer.

Aggregate safety data from 3 of the 5 company-sponsored clinical studies (phase 1 studies PRP-001 and PRP-002, and phase 2 study 673-201; N = 214 patients; data as of 30 Nov 2015) provide the basis for the most common treatment-emergent adverse events.

The most common adverse events associated with talazoparib (>20%) were myelosuppression (anemia, thrombocytopenia, neutropenia), gastrointestinal toxicity (nausea, diarrhea, vomiting), and fatigue. The most common grade 3 or higher adverse events and serious adverse events were associated with myelosuppression. A total of 25 of 214 patients had an adverse event that led to death (12 associated with underlying malignancies, 3 disease progression, 2 each lung infection and pneumonia, and 1 each cardiorespiratory arrest, neutropenic sepsis, renal impairment, dyspnea, hypoxia, and respiratory failure). Of these events, none was assessed as related to study drug. Eight of 214 patients discontinued study drug due to an adverse event.

In the ongoing phase 3 study 673-301, an adverse event of veno-occlusive disease of the liver leading to death was assessed as related to talazoparib by the investigator.

Additional information on the clinical safety of talazoparib is provided in the talazoparib investigator brochure.

1.2.3. Pharmacokinetics

The PK of talazoparib as a single agent was evaluated in 142 adult patients with cancer, including 109 patients with solid tumors (PRP-001) and 33 with hematologic malignancies (PRP-002). Doses of 0.025 mg to 2 mg were administered orally as a single dose or as once-daily doses. This dose range bracketed the 1 mg/day dose used in ongoing safety and efficacy studies, and provided a framework for assessing dose linearity. As the PK of talazoparib was similar in patients with solid tumors and hematologic malignancies, and no differences were apparent between males and females, the results are summarized collectively.

Oral absorption of talazoparib was rapid and independent of dose after administration of single or once-daily doses. Peak talazoparib concentrations were generally reached approximately 1 to 8 hours postdose. Exposure increased approximately dose-proportionally with increasing doses. At 1 mg/day, the mean half-life was approximately 2 days; the mean apparent volume of distribution (V/F) was 415 L, indicating extensive extravascular distribution. Steady state was reached in approximately 2 to 3 weeks with daily administration.

Apparent oral clearance (CL/F) of talazoparib appeared to be dose linear, with a mean CL/F across doses of approximately 5 L/h. Renal excretion was a major elimination pathway for unchanged parent talazoparib. Following oral administration, 44% to 90.6% of the dose was recovered in urine as unchanged parent drug over 24 hours at steady state for doses up to 1 mg/day. Mean renal clearance ranged from 1.38 L/h to 4.96 L/h independent of dose, suggesting linear urinary elimination kinetics.

Following repeated administration at 1 mg/day, talazoparib accumulated approximately 2.4-fold relative to a single dose. At steady state, the mean maximum plasma concentration (C_{max}) was 21.0 ng/mL, the mean plasma trough concentration (C_{min}) was 3.72 ng/mL, and the mean area under the plasma concentration-time curve (AUC) was 202 ng•h/mL.

PK data from a food-effect study showed that food had no effect on the extent of absorption of talazoparib (AUC) but decreased the rate of absorption (C_{max} was 46% lower and time to C_{max} [T_{max}] was 2.63 hours later); however this reduction in the rate of absorption following a single dose is not clinically relevant because talazoparib accumulates 2.4-fold at steady state after 1 mg once-daily dosing. Furthermore, AUC or C_{min} is thought to drive efficacy, not C_{max}; therefore, talazoparib can be taken with or without food. Talazoparib is being administered without regard to food in ongoing safety and efficacy studies.

A preliminary population PK analysis was performed with data from patients in studies PRP-001 and PRP-002 to assess the effects of renal function on PK parameters of talazoparib. Talazoparib CL/F in patients with mild renal impairment (creatinine clearance [CLCR] 60-89 mL/min) was similar compared with patients with normal renal function (CLCR ≥90 mL/min). In patients with moderate renal impairment (CLCR 30-59 mL/min), the talazoparib CL/F was decreased by 44% from normal, resulting in higher talazoparib exposure. Therefore, patients with moderate or severe renal impairment

(CLCR <60 mL/min) may be at risk of elevated exposure (≥50%) to talazoparib. The effects of hepatic impairment on talazoparib PK have not been studied.

The potential for talazoparib to affect the PK of other drugs was assessed through in vitro experiments and is described in Section 1.3.2.

Additional information on the PK of talazoparib is provided in the investigator brochure.

1.3. Summary of Relevant Nonclinical Experience With Talazoparib

1.3.1. Nonclinical Pharmacology of Talazoparib Monotherapy

The cytotoxic activity of talazoparib was demonstrated in cell culture, and antitumor effects were demonstrated in mouse xenograft models.

In cell-free enzyme assays, talazoparib inhibited PARP1 and PARP2 catalytic activity (Wang et al, 2016).[10] In vitro experiments showed that talazoparib was approximately 3- to 8-fold more potent at blocking PARP1 catalytic activity and up to 100-fold more potent at PARP trapping than other PARP inhibitors in clinical development (Murai et al, 2014; Shen et al, 2013).[6,8]

In tissue culture studies, talazoparib was cytotoxic to cancer cell lines harboring gene mutations that compromise DNA repair pathways, including MX-1 (BRCA1-mutant) and MDA-MB-468 (PTEN-mutant) mammary cancer cells, LNCaP (PTEN- and ATM-mutant) and PC-3 (PTEN-mutant) prostate cancer cells, and HCT-116 (MLH-1-mutant) colorectal tumor cells. The half-maximal inhibitory concentration (IC50) values of talazoparib in these cancer cell lines were in the single-digit nanomolar or subnanomolar range. The talazoparib IC50 for growth inhibition of Capan-1 pancreatic adenocarcinoma cells (BRCA2-deficient) was 50- to over 2000-fold lower than the other PARP inhibitors tested (Shen et al, 2013).[8]

The higher potency of talazoparib relative to the other PARP inhibitors is thought to be due to the more potent PARP trapping activity seen with talazoparib as opposed to inhibition of PARP catalytic activity (Shen et al, 2015).[9]

Talazoparib demonstrated potent antitumor activity in mouse xenograft models of small cell lung cancer (SCLC) (Cardnell et al, 2013)[1] and a mammary cancer xenograft (Shen et al, 2013).[8]

Additional information on the nonclinical pharmacology of talazoparib is provided in the talazoparib investigator brochure.

1.3.2. Nonclinical PK and Metabolism

PK studies in rats and dogs show that talazoparib oral bioavailability was >43% in rats and >51% in dogs. A Good Laboratory Practice (GLP) study in dogs demonstrated that the capsule formulation used in clinical studies is approximately 2-fold more bioavailable than the suspension formulation used in nonclinical studies. In general, talazoparib displays greater than or approximately dose-proportional increases in exposure in rats and dogs with no evidence of sex differences.

Studies of [^{14}C]-talazoparib in rats and dogs indicate rapid absorption, wide distribution (greater than total body water), and nearly complete elimination of drug substance (>90%) by 7 days. Fecal elimination was the main route of elimination in both species, and renal excretion was moderate (21-26%). In a study in rats, [^{14}C]-talazoparib was widely distributed, reaching maximum levels 1 to 4 hours postdose. Excluding the gastrointestinal tract, the highest radioactivity levels were observed in liver and kidney (and the eye uveal tract in albino rats). Tissue radioactivity levels were greater than blood levels in the target organs of talazoparib toxicity (bone marrow, spleen, and thymus) through 7 days. Metabolic profiling of plasma, urine, and feces samples indicated that [^{14}C]-talazoparib is largely cleared via excretion of unchanged parent drug and metabolized to a minor extent via oxidation and dehydrogenation.

In vitro metabolism studies in rat, dog, and human hepatic microsomes demonstrated that [14C]-talazoparib has high metabolic stability (>90%) over 2 hours. A minimal extent or a lack of metabolism for [14C]-talazoparib was observed in the presence of freshly isolated mouse, rat, dog, and human hepatocytes or cryopreserved human hepatocytes. Talazoparib does not appear to be a substrate of any major cytochrome P450 (CYP450) metabolizing enzyme.

Mean binding to human plasma proteins is 78.7%; therefore, it is unlikely that talazoparib will demonstrate clinically significant drug-drug interactions related to displacement from plasma protein binding sites. At therapeutic exposures, talazoparib does not markedly induce or inhibit CYP450 enzymes. Therefore, it is unlikely that talazoparib will demonstrate clinically significant CYP450 inhibition- or induction-based drug-drug interactions when coadministered with corresponding substrates. At therapeutic exposures, talazoparib does not markedly induce or inhibit any transporters. Therefore, it is unlikely that talazoparib will demonstrate clinically significant drug transporter inhibition-based drug–drug interactions when coadministered with corresponding substrates.

Because talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), plasma talazoparib concentrations may increase or decrease when coadministered with P-gp or BCRP inhibitors or inducers, respectively. Guidelines for concomitant use of talazoparib inhibitors or inducers of P-gp or inhibitors of BCRP are provided in Section 7.3.

Additional information on the nonclinical PK and drug metabolism of talazoparib is provided in the investigator brochure.

1.3.3. Nonclinical Toxicology

Safety pharmacology, single- and repeat-dose toxicity, genotoxicity, embryo-fetal development, and in vitro phototoxicity studies were conducted to evaluate the nonclinical toxicology profile of talazoparib. Repeat-dose toxicity/toxicokinetic studies were conducted with talazoparib utilizing the intended oral route of administration in mice, rats, and dogs. A repeat-dose study with talazoparib was conducted in BALB/c nude mice to select doses and exposures for the mouse xenograft studies.

Five-day, 28-day, and 13-week repeat-dose GLP toxicity and toxicokinetic studies with 28-day recovery periods were conducted in the rat and dog. The major findings are as follows:

- Dose-dependent pancytopenia with bone marrow hypocellularity and depletion of lymphoid tissue in multiple organs was observed and considered possibly due to exaggerated pharmacology of talazoparib based on the higher (relative to baseline) poly(ADP-ribose) (index of PARP1/2 activity) tissue levels in these organs. The hematologic findings were partially reversible and may be readily monitored in the clinic. The toxicities that resulted in mortality in dogs (0.1 mg/kg/day) and some rats (1 mg/kg/day) occurred at AUC0-24 exposures that were >0.8- and 4-fold higher, respectively, than the exposure at the recommended human dose of 1 mg/day. The toxicities were mainly due to septicemia that resulted from the severe bone marrow and lymphoid depletion;

- A dose-dependent increased incidence of gastrointestinal tract findings of apoptosis/necrosis in the stomach and duodenum was observed. Additional findings at higher doses included reversible villous atrophy and increased apoptosis throughout the gastrointestinal tract, most notably in the small intestine. Gastrointestinal tract toxicities of enteropathy and villous atrophy caused mortality in rats at 3.0 mg/kg/day. Exposures at 3.0 mg/kg/day are significantly higher than the exposures at the recommended human dose;

- Additional findings at the high dose (≥1 mg/kg/day) in the 5-day GLP study in rats included focal necrotic changes in the ovarian follicular atresia and hepatocyte necrosis of the liver. These findings were not observed in the 28-day or 13-week repeat-dose studies in rats;

- Atrophy and/or degenerative changes in testes and epididymis and effects on the seminiferous tubules were observed in rats and dogs; the severity correlated with both dose and duration of treatment.

There were no talazoparib-related effects on respiratory or central nervous system parameters after a single oral administration to rats (safety pharmacology studies), or on cardiovascular parameters and electrocardiogram evaluations after a repeat-dose oral administration in dogs (repeat-dose toxicity studies). Talazoparib had no effect on ophthalmologic end points in rats or dogs in repeat-dose toxicity studies. Talazoparib was not mutagenic in a bacterial reverse mutation assay, but consistent with the genomic instability of its primary pharmacology, was clastogenic in an in vitro chromosomal aberration assay and an in vivo micronucleus assay, indicating the potential for genotoxicity in humans. Talazoparib caused fetal malformations, structural variations, and death in an embryo-fetal development study in rats. Based on an in vitro 3T3 neutral red uptake assay, which results in a high incidence of false positives, talazoparib is potentially phototoxic in humans. In conclusion, the main nonclinical toxicologic findings were early hematologic changes and subsequent bone marrow and lymphoid organ depletion; focal atrophy and degeneration of testes, epididymis, and seminiferous tubules; and dose-dependent apoptosis/necrosis in the gastrointestinal tract and liver after repeat-dose talazoparib. These findings are consistent with the exaggerated pharmacology of talazoparib and its tissue exposure pattern.

Additional information on the toxicology of talazoparib is provided in the talazoparib investigator brochure.

1.4. Talazoparib Benefits and Risks Assessment

The doses of talazoparib in this protocol are supported by nonclinical studies and phase 1 studies in patients with advanced malignancies. Antitumor activity has been observed in these studies and is being further evaluated in a larger patient population. Common adverse events with talazoparib as monotherapy include myelosuppression, gastrointestinal toxicity, fatigue, and alopecia. Myelodysplastic syndrome/Acute Myeloid Leukemia, hepatotoxicity, second primary malignancies (other than hematologic), and pneumonitis are additional rare and serious adverse events of special interest per the investigator's brochure, Section 7. 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, which is the single reference safety document (SRSD) for this study.

2. STUDY OBJECTIVE

- To obtain additional safety data on long-term talazoparib use.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

This is a single-arm, open-label, extended treatment, safety study in patients treated with talazoparib (also known as MDV3800, BMN 673, PF-06944076) as a single agent or in combination with another agent in qualifying originating clinical studies sponsored by Medivation/Pfizer. The safety and tolerability of long-term talazoparib use will be evaluated,

and the data collected will be limited to safety assessments. The study provides access to single-agent talazoparib for qualifying patients who may benefit from continuing therapy with talazoparib.

Eligible patients must have received talazoparib in a qualifying study and have no ongoing grade 3 or 4 talazoparib-related toxicities. Patients must receive their first dose of talazoparib in this protocol within 2 months after their last dose of talazoparib in the originating study and may not receive any intervening antineoplastic therapies before starting this study. Patients will have clinic visits approximately every 4 weeks for the first 24 weeks and then approximately every 8 weeks thereafter (additional visits for laboratory testing every 2 weeks through week 9 and every 4 weeks thereafter) or as clinically indicated. Patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study (eg, if a PRP-001 patient is on an every 4 week schedule in the originating study, the patient is required to complete the week 5 and week 9 visits but not the CBC assessments at week 3 and week 7; afterwards, these patients would follow the schedule of activities in Appendix 1). Additional clinic visits and laboratory testing may be necessary to monitor safety (eg, for dose modification, hematologic toxicity, pregnancy testing).

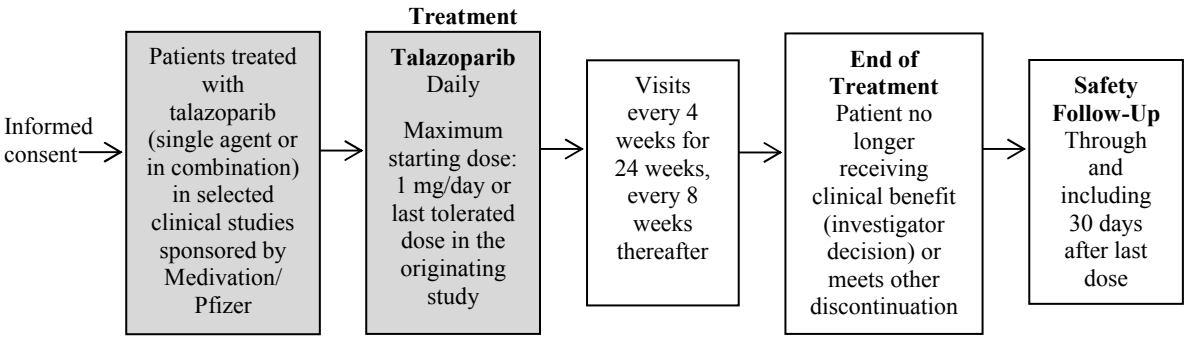
The maximum starting dose of talazoparib will be 1 mg/day or the last tolerated dose administered in the originating study. Talazoparib capsules will be administered by mouth once daily with or without food at approximately the same time of day. Patients receiving talazoparib as combination treatment in the originating study will receive talazoparib as a single agent in this extended treatment study. Talazoparib administration may continue as long as the investigator considers treatment to be providing clinical benefit or until other study discontinuation criteria are met (Section 5.3). The addition of any other antineoplastic therapy and the concurrent use of investigational agents during the study are prohibited.

Study assessments will include adverse events, local clinical laboratory tests, concomitant medications, physical examinations, and vital signs (and weight). Clinical laboratory tests (hematology, serum chemistry) will be performed every 4 weeks through week 25 and every 8 weeks thereafter during the study. Complete blood count (CBC) tests will be completed every 2 weeks through week 9 and every 4 weeks thereafter. Women of childbearing potential must have a pregnancy test every 4 weeks. Safety follow-up will be through and including 30 days after the last dose of talazoparib.

3.2. Study Schematic

The study schematic is provided in Figure 1.

Figure 1. Study Schematic



Key assessments: laboratory tests, physical examinations, adverse events.
Patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study.

3.3. Blinding

All talazoparib treatment will be open label. All patients, study site personnel (including investigators), and sponsor staff and its representatives will be unblinded to treatment identity.

3.4. Duration of Study

Talazoparib administration will continue until the last patient has stopped deriving clinical benefit as assessed by the investigator or meets other study discontinuation criteria (Section 5.3). The total duration of this study is anticipated to be approximately 4 years.

3.5. Discussion of Study Design

This study is designed to evaluate the safety and tolerability of long-term talazoparib use for patients who were treated with talazoparib as a single agent or in combination with another agent in a qualifying talazoparib clinical study who may benefit from continuing therapy with talazoparib. Talazoparib is considered a cytotoxic and clastogenic agent and therefore, cannot be administered to healthy volunteers. Only patients with cancer may be enrolled in talazoparib studies, including phase 1 and clinical pharmacology studies, which generally include only a single dose or very short dosing periods.

3.5.1. Rationale for Dose and Schedule

Patients will receive talazoparib at a maximum starting dose of 1 mg/day or the last tolerated dose administered in the originating study. The maximum tolerated dose of talazoparib is 1 mg/day and is the recommended phase 2 monotherapy dose based on the results of the phase 1, dose-escalation study in patients with solid tumors (PRP-001). However, patients whose last tolerated dose of talazoparib was reduced from 1 mg/day in the originating study will continue to receive the reduced dose in this study. The maximum dose of talazoparib allowed for patients with moderate renal impairment (defined as estimated Glomerular Filtration Rate (eGFR) ≥30 and ≤59 mL/min/1.73m^2) is 0.75 mg/day. The maximum dose of talazoparib allowed for patients with severe renal impairment (defined as eGFR ≥15 and ≤29 mL/min/1.73m^2, not on dialysis) is the last tolerated dose on the originating study up to a maximum dose of 0.5 mg/day.

4. SELECTION OF STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. Treated with talazoparib as a single agent or in combination with another agent in a qualifying talazoparib clinical study in advanced solid tumors sponsored by Medivation/Pfizer and has no ongoing National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 talazoparib-related toxicities.

2. Willing and able to provide informed consent for extended open-label treatment.

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

4. Able to swallow capsules whole, have no known intolerance to talazoparib or excipients, and able to comply with study requirements throughout the study.

5. Able to tolerate ≥0.25 mg/day talazoparib during the originating study.

6. Female patients of childbearing potential (defined in Section 4.3) must have a negative pregnancy test before the first dose of talazoparib and must agree to use a highly effective birth control method (defined in Section 4.3) from the time of the first dose of talazoparib through 7 months after the last dose.

7. Male patients must use a condom when having sex with a pregnant woman or with a woman of childbearing potential from the time of the first dose of talazoparib through 4 months after the last dose. Contraception should be considered for a nonpregnant female partner of childbearing potential.

8. Female patients may not be breastfeeding at the first dose of talazoparib and must not breastfeed during study participation through 7 months after the last dose of talazoparib.

9. Male and female patients must agree not to donate sperm or eggs, respectively, from the first dose of talazoparib through 4 and 7 months, respectively, after the last dose.

4.2. Exclusion Criteria

Each patient eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. Permanently discontinued from any Medivation/Pfizer-sponsored study with talazoparib alone or in combination with another agent.

2. Received an antineoplastic therapy or investigational agent after treatment with talazoparib in the originating study.

3. Has a clinically significant cardiovascular, dermatologic, endocrine, gastrointestinal, hematologic, infectious, metabolic, neurologic, psychologic, or pulmonary disorder or any other condition, including excessive alcohol or drug abuse, or secondary malignancy, that may interfere with study participation in the opinion of the investigator.

4. Diagnosis of myelodysplastic syndrome (MDS).

5. For patients entering from studies MDV3800-01 (renal impairment) or MDV3800-02 (hepatic impairment), clinically significant deterioration of renal or hepatic function, respectively, after dosing in the originating study.

6. Serious accompanying disorder or impaired organ function, including the following:

    - Renal: Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 by the MDRD equation (Modification of Diet in Renal Disease [available via www.mdrd.com]), except for patients from study MDV3800-01 (renal impairment) with severe renal impairment (eGFR 15-29 mL/min/1.73 m2).

    - Hepatic:

        - For patients entering from all other qualifying studies excluding MDV3800-02 (hepatic impairment): Total serum bilirubin >1.5 times the upper limit of normal (ULN) (>3 × ULN for patients with Gilbert syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation). Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 times ULN (if liver test abnormalities are due to hepatic metastases, AST or ALT ≥5 × ULN).

        - For patients entering from study MDV3800-02 (hepatic impairment): Inability to tolerate talazoparib 0.25 mg/day or had liver tests (bilirubin, AST, or ALT) that worsened to clinically significant values during the study.

    - Bone marrow reserve (Blood samples collected after at least 14 days without growth factor support or transfusion. Dose modification in the originating study is permitted to improve bone marrow reserve for eligibility):

        - For patients entering from all qualifying studies excluding patients with moderate or severe hepatic dysfunction (Groups C and D) of study MDV3800-02 (hepatic impairment): Absolute neutrophil count <1500/µL, platelets <100,000/µL, or hemoglobin <9 g/dL.

- For patients with moderate or severe hepatic dysfunction (Groups C and D) entering from study MDV3800-02 (hepatic impairment): Absolute neutrophil count <1500/μL, platelets <50,000/μL, or hemoglobin <8 g/dL.

4.3. Reproductive Considerations

Female patients of childbearing potential must have a negative serum pregnancy test before the first dose of talazoparib and a negative urine or serum test every 4 weeks thereafter during the treatment period and must avoid pregnancy during the study. Urine pregnancy tests must have a limit of detection of 25 IU/L (or equivalent units) for human chorionic gonadotropin. If a pregnancy test is positive, talazoparib will be discontinued.

Female patients of childbearing potential must use a highly effective form of birth control from the first dose of talazoparib through 7 months after the last dose, defined as follows:

- Established use of an oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
- Established use of an oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
- Placement of an intrauterine device or intrauterine hormone-releasing system;
- Bilateral tubal ligation for ≥6 months before the first dose of talazoparib in the current study;
- Partner vasectomized for ≥6 months before the first dose of talazoparib in the current study;
- Sexual abstinence when in relation to the preferred and usual lifestyle of the patient.

Female patients who meet 1 of the following criteria are considered not of childbearing potential:

1. Surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy); OR
2. Postmenopausal, defined as follows:
    - ≥55 years of age with no spontaneous menses for ≥12 months before the first dose of talazoparib in the current study;
    - <55 years of age with no spontaneous menses for ≥12 months before the first dose of talazoparib in the current study and with a postmenopausal follicle-stimulating hormone (FSH) concentration >30 IU/L.

Male patients must use a condom when having sex with a pregnant woman or with a woman of childbearing potential from the first dose of talazoparib through 4 months after the last dose. Contraception should be considered for a nonpregnant female partner of childbearing potential.

Details regarding the reporting procedures to follow in the event of pregnancy are provided in Section 8.4.3.1 Instructions regarding egg donation and breastfeeding are provided in Section 4.1.

5. ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The study periods will include treatment and safety follow-up. The timing of all study procedures is provided in the schedules of activities (Appendix 1). Signed informed consent must be obtained before performing any study-specific procedures.

The informed consent may be signed and eligibility may be evaluated while the patient is participating in the originating study and may be completed greater than 28 days prior to the week 1 visit. The Interactive Response Technology (IRT) system user manual contains the information needed for registering patient status.

5.1. Informed Consent and Eligibility

Study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures were part of the originating study or routine standard of care, and must document the informed consent process in the patient's source documents. The informed consent form must be signed before any study-specific procedures and eligibility testing must be completed within 28 days before the week 1 visit. Any eligibility testing procedures completed for the originating study within 28 days prior to the week 1 visit in this study may be used to assess eligibility for this study as applicable.

Patients will be identified with the patient number used in the originating study. After obtaining signed informed consent, study site personnel will evaluate potential study participants for eligibility.

The investigator will assess the eligibility of each patient. All relevant information must be available before eligibility can be determined. Eligibility assessments include ECOG status, adverse events, physical examination, pregnancy test (female patients of childbearing potential only), and hematology and serum chemistry tests. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After the investigator determines the patient is eligible for the study, study site personnel will complete an Enrollment Authorization Form and email it to the medical monitor or designee ideally 2 business days before the anticipated week 1 visit to approve the enrollment in writing. Study site personnel should ensure that an approved Enrollment Authorization Form is in the patient's file before proceeding with week 1 procedures.

5.2. Treatment Period

5.2.1. Treatment Period Visit Windows

All treatment period visits have a visit window of ±7 days (ie, 7 days before or after the given day), except the week 1 visit (assessment of eligibility and start of study treatment), which has a visit window of -28 days.

Talazoparib supplies (and the relative total number of capsules provided each time) must be taken into account when scheduling visits during visit windows to ensure patients do not run out of study drug between visits. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

5.2.2. Treatment Period Study Visit Procedures

For the purpose of this study, there will be no day 0.

During the week 1 visit, the investigator will determine whether the patient is eligible for the study (Section 5.1) and the patient will start study treatment. Day 1 is the day of the first dose of talazoparib in this study, which will occur within 2 months after the last dose in the originating study.

All patients will have visits approximately every 4 weeks for the first 24 weeks and then approximately every 8 weeks thereafter or as clinically indicated (additional visits for laboratory testing every 2 weeks through week 9 and every 4 weeks thereafter). Patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study (eg, if a PRP-001 patient is on an every 4 week schedule in the originating study, the patient is required to complete the week 5 and week 9 visits but not the CBC assessments at week 3 and week 7; afterwards, these patients would follow the schedule of activities in Appendix 1).

Specified study procedures will be performed at each clinic visit according to the schedule of activities (Appendix 1).

Clinical laboratory assessments will be conducted and reviewed before dosing at each visit. Any clinically significant abnormalities must be reported as adverse events per CTCAE, version 4 criteria. Dose modifications will be made as necessary Section 9.1.1).

Potential hematologic toxicities will be monitored by completing CBC tests every 2 weeks through week 9 and every 4 weeks thereafter (if abnormal, refer to Section 9.1.1).

Female patients of childbearing potential must have a negative serum pregnancy test before the first dose of talazoparib and a negative urine or serum test every 4 weeks thereafter before dosing.

Study visits and talazoparib treatment will continue as long as the investigator considers treatment to be providing clinical benefit or until other study discontinuation criteria are met (Section 5.3).

5.2.3. Unscheduled Visit Procedures

Unscheduled visits may be performed anytime to assess or follow up adverse events, for dose modification, or at the request of the patient or investigator. The date and reason for the unscheduled visit must be recorded in the source documentation.

A review of adverse events and changes to concomitant medications or treatments (including herbal therapies) occurring since the previous visit should be performed at unscheduled visits. If an unscheduled visit is necessary to assess toxicity, diagnostic tests may be performed based on investigator assessment as appropriate.

Unscheduled visit procedures are listed in Appendix 1. Other study procedures may be performed as clinically appropriate.

5.3. Permanent Treatment Discontinuation

Permanent treatment discontinuation is defined as cessation of talazoparib administration. After permanent discontinuation, safety follow-up will be per Section 5.4, unless the patient withdraws consent for further follow-up.

Temporary treatment interruption (eg, due to an adverse event) is not considered permanent discontinuation.

The primary reasons for which patients *permanently discontinue* study treatment are listed in Table 1.

Table 1. Primary Reasons For Permanent Treatment Discontinuation

Reason	Comment
Disease progression	Talazoparib treatment will be discontinued if the investigator believes that talazoparib is no longer providing clinical benefit.
Adverse event or intercurrent illness	Any intolerable adverse event that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the investigator or sponsor would lead to undue risk if study treatment were continued (eg, severe drug induced liver injury Section 9.1.2.1 or myelodysplastic syndrome [MDS]/acute myeloid leukemia [AML] [Table 4]). Refer to Section 8.2.1. May or may not be related to disease progression.
Administration of prohibited concomitant therapy	Refer to Section 7.2.
Patient decision	Patients may permanently discontinue treatment anytime for any reason.
Investigator decision	The investigator may elect to discontinue talazoparib if in their opinion it is in the patient's best interest. This category should be selected if adverse event or administration of prohibited concomitant therapy do not apply and the patient preferred to continue treatment.

Major noncompliance with protocol	The medical monitor or investigator may request permanent treatment discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance.
Loss to follow-up	Refer to Section 5.5.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime for any reason as described in Section 13.6. The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

5.4. Safety Follow-Up

Patients will have safety follow-up after permanent discontinuation of talazoparib. Safety follow-up should occur through and including 30 days after the last dose of talazoparib.

Safety follow-up procedures are listed in Appendix 1.

If treatment is discontinued due to an adverse event or serious adverse event, the event(s) must be followed up as described in Section 8.1.4.1.

For patients who refuse to come to the clinic for safety follow-up, telephone contact must be attempted and documented to review for adverse events through approximately 30 days after the last dose of talazoparib. If the patient does not respond to telephone calls, the procedures for loss to follow-up in Section 5.5 should be followed.

5.5. Loss to Follow-Up

Every reasonable effort must be made to contact any patient apparently lost to follow-up during the course of the study to complete study-related assessments and record outstanding data. Following unsuccessful telephone contact, the following should occur:

- An effort to contact the patient by mail using a method that provides proof of receipt should be attempted.
- Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives).
- Such efforts should be documented in the patient's source documents.

If all efforts fail to establish contact, the patient will be considered lost to follow-up. Patients who withdraw consent will be considered lost to follow-up for analysis purposes.

6. INVESTIGATIONAL PRODUCT INFORMATION

6.1. General Information

The study drug is talazoparib. The sponsor will provide talazoparib capsules.

6.2. Talazoparib Product Characteristics

Talazoparib is provided as the 4-methylbenzenesulfonate (tosylate) salt and has the chemical name (8S,9R) 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1H-1,2,4-triazol-5-yl)-3H-pyrido[4,3,2-de]phthalazin-3-one. The drug product is a capsule containing talazoparib tosylate and silicified microcrystalline cellulose. The capsules for each dose strength will be provided in dose-specific colors. Additional details will be provided in the Investigational Product (IP) Manual.

6.2.1. Packaging of Talazoparib

Talazoparib study drug is packaged in induction sealed, high-density polyethylene bottles with child-resistant caps.

The label will vary depending on individual country requirements. At minimum, each label typically provides the study protocol number, contents, directions for use, storage directions, clinical trial statement, sponsor name, batch/lot number, and product retest or expiration date.

6.2.2. Storage and Handling of Talazoparib

The drug product should be stored safely and properly in accordance with the study drug label.

Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including disposable gloves, and equipment (Goodin et al, 2011).[2] Patients should be advised that oral anticancer agents are toxic substances and that other caregivers should always use gloves when handling the capsules.

6.2.3. Directions for Administration of Talazoparib

The maximum daily dose of talazoparib is 1 mg/day given orally at approximately the same time each day. For patients who last tolerated a reduced dose in the originating study, the last tolerated dose will be given as the daily dose in this study. The maximum dose of talazoparib allowed for patients with moderate renal impairment (defined as eGFR $\geq$30 and $\leq$59 mL/min/1.73m^2) is 0.75 mg/day. The maximum dose of talazoparib allowed for patients with severe renal impairment (defined as eGFR $\geq$15 and $\leq$29 mL/min/1.73m^2, not on dialysis) is the last tolerated dose on the originating study up to a maximum dose of 0.5 mg/day.

Patients should self-administer talazoparib orally once daily, with or without food. The capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening them.

Patients should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed.

Medication errors for this study include:

- Medication errors involving patient exposure to the investigational product:
  - Lack of dose reduction as specified by the protocol;
  - Continuation of treatment although patient met discontinuation criteria;
  - Incorrect study drug dose taken by patient;
  - Patient did not take study medication for 6 or more days (approximately <80% compliance) within 4 weeks, unless dose withheld due to an AE;
  - Patient did not receive treatment as assigned by IRT.
- Potential medication errors or used outside of what is foreseen in the protocol that do or do not involve the participating patient.

Refer to Section 8.4.4 for instructions on how to report a medication error.

6.2.3.1. Dose Modifications

Dose modifications for talazoparib due to adverse events are described in Section 9.1.1.

Talazoparib dose escalation at 0.25 mg increments up to the maximum protocol specified dose of 1.0 mg/day may be allowed at the next visit if the following conditions are all met:

- The reduced dose is tolerated and any toxicities are resolved;
- Dose re-escalation has been agreed with the medical monitor prior to implementation of the dose escalation;
- Dose escalation for patients with moderate renal impairment (defined as eGFR ≥30 and ≤59 mL/min/1.73 m^2) may be allowed up to a maximum dose of 0.75 mg/day;
- Dose escalation for patients with severe renal impairment (defined as eGFR ≥15 and ≤29 mL/min/1.73m^2, not on dialysis) may be allowed up to the last dose tolerated in the originating study up to a maximum dose of 0.5 mg/day;
- Dose escalation for patients that are coadministered a strong P-gp inhibitor, may be allowed up to a maximum dose of 0.75 mg/day.

Dose modifications due to adverse events are described in Section 8.2.1.

6.2.3.2. Overdose Management

An overdose is defined as any dose greater than the protocol-specified maximum starting dose.

There is no specific treatment in the event of talazoparib overdose, and symptoms of overdose are not established. In the event of overdose, treatment with talazoparib should be stopped, and physicians should consider gastric decontamination, follow general supportive measures and treat symptomatically taking into consideration the mean half-life is 89.9 hours. All overdose events are to be reported within 24 hours of awareness by the study site according to Section 8.4.4 whether or not the overdose is associated with an adverse event and the sponsor/medical monitor must be contacted.

6.3. Treatment Compliance

Accountability for the talazoparib capsules will be performed to document compliance with the dosing regimens. Patients will be asked to bring all used and unused talazoparib bottles to study visits. Study site personnel must make reasonable efforts to obtain used and unused talazoparib bottles from patients who do not routinely return them at study site visits.

Unreturned capsules will be considered to have been taken.

7. PRIOR AND CONCOMITANT THERAPY

Prior and concomitant medications include all vitamins, herbal remedies, and over-the-counter and prescription medications.

7.1. Prior Medications

Medications taken after the last dose of talazoparib in the originating study and before the first dose of talazoparib in the current study, and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, must be recorded on the case report form and in the patient's source documents.

Per the study eligibility criteria (Section 4), patients who received an antineoplastic therapy or investigational agent after treatment with talazoparib in the originating study are excluded from study participation.

7.2. Concomitant Therapy

Concomitant therapy (noninvestigational products) includes any concomitant medications, blood transfusions, or radiotherapy used between day 1 and safety follow-up.

Palliative radiation is allowed during the study, but the combination of radiation therapy and talazoparib as monotherapy has not been studied.

Concomitant medications will be assessed at all clinic visits (excluding weeks 3 and 7 and every 4 weeks after week 25 when only CBC testing is scheduled). All concomitant medications, including over-the-counter and prescription medications, must be recorded on the appropriate case report form. If the use of any medication during the study is due to an adverse event, the adverse event must be recorded on the adverse event case report form and in the patient's source documents.

Prohibited medications are described in Table 2. Deviation from these guidelines should occur only if absolutely necessary for the well-being of the patient, and the medical monitor is to be notified to determine whether continued treatment with talazoparib is permitted.

Talazoparib must be permanently discontinued upon initiation of a new antineoplastic therapy. Patients who discontinue treatment due to initiation of such therapy will complete safety follow-up per Section 5.4.

Table 2. Prohibited Concomitant Therapies

Medication or Treatment	Comment on Use
Any antineoplastic therapy (including biologic, radionuclide)	Any time after treatment in the originating study through safety follow-up.
Other investigational agent (eg, biologic, vaccine, or other agents not approved for marketing)	Any time after treatment in the originating study through safety follow-up.
Live bacterial and virus vaccines	

7.3. Potential Interactions Between Talazoparib and Concomitant Medications

Talazoparib is a substrate for drug transporters P-gp and BCRP and mainly eliminated by renal clearance as unchanged compound. P-gp inhibitors, P-gp inducers, and BCRP inhibitors may affect talazoparib plasma concentrations.

Guidelines for concomitant use of talazoparib with inhibitors or inducers of P-gp or inhibitors of BCRP are as follows:

- Use of strong P-gp inhibitors (including but not limited to amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar, and verapamil) is not recommended. If patients must be coadministered a strong P-gp inhibitor, the maximum dose of talazoparib should be 0.75 mg/day.
- Use of P-gp inducers (including but not limited to carbamazepine, rifampin, and St. John's wort) and BCRP inhibitors (including but not limited to curcumin, cyclosporine, and elacridar,[GF120918]) should be avoided. Refer to the following website for a complete list: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

The sponsor/medical monitor should be consulted prior to a patient taking strong a P-gp inhibitor, a P-gp inducer, or a BCRP inhibitor.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the Case Report Form (CRF) and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All for all enrolled patients*	All
Non-serious AE	All for all enrolled patients*	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

* Please note that AEs including SAEs for all enrolled patients that occur between consent for this study and first dose in this study are to be recorded on the Medical History CRF and not as AEs. AEs are recorded in the qualifying originating study as AEs, if occurring during the active collection period of the qualifying originating study.

All observed or volunteered events regardless of suspected causal relationship to the investigational product will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded in the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient/parent(s)/legal guardian/legally acceptable representative. In addition, each study patient/parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Permanent Treatment Discontinuation section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient takes the first dose of study drug (investigational product) through and including a minimum of 30 calendar days after the last administration of the investigational product. Adverse events including SAEs for all enrolled patients that occur between when patient provides informed consent for this study, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product) and first dose in this study are to be collected on the Medical History CRF for this study and not as AEs and collected/reported in the qualifying originating study as AEs.

For patients who are screen failures, the active collection period ends when screen failure status is determined. No data is to be entered in the CRF for screen failures for this study; however, SAEs must still be reported to Pfizer safety within 24 hours for screen failures.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

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

If a patient 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.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs for all enrolled patients are recorded on the CRF. As noted above, AEs including SAEs for all enrolled patients that occur between consent for this study and first dose in this study are to be recorded on the Medical History CRF and not as AEs. AEs are recorded in the qualifying originating study as AEs, if occurring during the active collection period of the qualifying originating study.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious) occurring after the first dose of study drug in this study; the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

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.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

Additionally, for this study important medical events include:

- A diagnosis of MDS or acute myeloid leukemia (AML). Tissue samples and any other supporting data used to enable the diagnosis of MDS or AML should be submitted for central review if requested.
- Second primary malignancy
- Abnormal liver test results (in addition to the requirement for Potential Cases of Drug-Induced Liver Injury, Section 8.4.2), as described below:
    - AST or ALT ≥3 times ULN (>5 × ULN if baseline ALT/AST is >3 × ULN) and total bilirubin >2 times ULN or INR >1.5;
    - AST or ALT ≥3 times ULN with signs and symptoms consistent with hepatitis and/or eosinophilia (≥500 eosinophils/µL).

Important medical events occurring during the safety reporting period must be reported within 24 hours of awareness by the study site using a CT SAE report form.

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 Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);

- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the *CRF*, the investigator will use the following definitions of severity in accordance with the current CTCAE version to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. 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 patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (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 lab 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 patient's individual baseline values and underlying conditions. Patients 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:

- Patients 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 patients 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 patient 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. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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 (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) 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.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, 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. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes 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 investigational product.

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 patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient 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.

8.4.4. Medication Errors

Other exposures to the investigational product 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

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Such medication errors occurring to a study patient 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 immediately.

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 non-serious, are recorded on an 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**.

9. ASSESSMENT OF SAFETY ENDPOINTS

Study assessments will include adverse events, physical examinations, vital signs (and weight), and clinical laboratory tests. The procedures for the investigator assessment of adverse events are presented in detail in Section 8. The procedures for clinical laboratory safety tests are presented in Section 9.1, and for physical examinations and vital signs in Section 9.2.

9.1. Clinical Laboratory Tests

Routine clinical laboratory tests (hematology, serum chemistry) will be performed according to the schedules of activities (Appendix 1). Samples will be stored until the specified analyses are completed and then will be destroyed in accordance with standard laboratory practice and applicable local regulations.

A list of the required routine clinical laboratory tests and other evaluations is provided in Table 3. All samples for laboratory analysis must be collected, prepared, and labeled according to laboratory requirements.

All clinical laboratory tests will be performed by the local laboratory. The local laboratory reference ranges will be used.

Table 3. Clinical Laboratory Tests

Hematology	Chemistry	Additional Tests
Hematocrit Hemoglobin Mean corpuscular volume Red blood cell count Platelet count White blood cell count with differential • Total neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	Albumin Total protein Alkaline phosphatase ALT (alanine aminotransferase) AST (aspartate aminotransferase) Total bilirubin Blood urea nitrogen Creatinine Glucose (nonfasting) Bicarbonate Calcium Chloride Magnesium Phosphate Potassium Sodium LDH (lactate dehydrogenase)	Serum and urine pregnancy tests for women of childbearing potential

9.1.1. Dose Modifications Due to Adverse Events

Table 4. Talazoparib Dose Modifications Due To Adverse Events

Toxicity	Management of Adverse Events (Except Liver Abnormalities[1])
Grade 1 or 2	No requirement for dose interruption or dose reduction.
Selected hematologic grade 3 or 4 events	
Anemia (hemoglobin <8.0 g/dL)	Hold talazoparib and monitor weekly until hemoglobin returns to ≥9 g/dL (for patients originating from Groups C or D of study MDV3800-02: hold talazoparib and monitor at least twice weekly until hemoglobin returns to ≥ 8 g/dL). Implement supportive care per local guidelines. • Talazoparib may be reduced by 1 dose level as described in Table 5. If anemia persists for >4 weeks without recovery to ≥9g/dL (to ≥8 g/dL for patients originating from Groups C or D of study MDV3800-02), discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Toxicity	**Management of Adverse Events (Except Liver Abnormalities[1]**
Neutropenia (ANC <1000/µL)	Hold talazoparib and monitor weekly until ANC ≥1500/µL. Implement supportive care per local guidelines. Resume talazoparib based on the following recovery times: • ≤1 week: No change. • >1 week: Reduce talazoparib by 1 dose level as described in Table 5. If neutropenia persists for >4 weeks without recovery to ≥1500/µL, discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Thrombocytopenia (platelets <50,000/µL)	Hold talazoparib until platelets ≥75,000/µL (for patients originating from Groups C or D of study MDV3800-02: hold talazoparib and monitor at least twice weekly until platelets return to ≥ 50,000/ µL). Implement supportive care per local guidelines. Resume talazoparib based on the following recovery times: • ≤1 week: No change. • >1 week: Reduce talazoparib by 1 dose level as described in Table 5. If thrombocytopenia persists for >4 weeks without recovery to ≥75,000/µL (to ≥50,000/ µL for patients originating from Groups C or D of study MDV3800-02), discontinue talazoparib and refer to a hematologist for evaluation, including assessment for possible MDS/AML.
Other grade 3 or 4 events, except abnormal liver tests[1]	Hold talazoparib as follows: • For clinically significant grade 3 or 4 laboratory abnormalities, talazoparib may be held. Resume talazoparib when the laboratory abnormality resolves to grade ≤2 (baseline grade for creatinine increases). • For clinically significant grade 3 or 4 adverse events, hold talazoparib until the adverse event resolves to grade ≤2. Resume talazoparib at the same dose or reduce by 1 dose level as described in Table 5 if the event resolves or improves within 4 weeks of holding talazoparib, and can be monitored if it recurs. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Talazoparib should be permanently discontinued for unresolved grade 3 or 4 toxicity per investigator decision that continued talazoparib treatment is not in the patient's best interest.

1. Dose modifications for liver abnormalities are discussed in Table 6.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; MDS, myelodysplastic syndrome.

NOTE: Patients originating from Groups C or D of study MDV3800-02 with hemoglobin ≥8 and <9 g/dL and/or platelet count ≥50,000 and <100,000/μL at study entry, need to be able to maintain values at ≥8 g/dL and ≥50.000/μL, respectively, during the study. Upon second dose interruption due to drop in hemoglobin and/or platelet count below 8 g/dL and below 50.000/μL, respectively, they need to permanently discontinue study treatment.

The dose of talazoparib may be reduced incrementally as shown in Table 5.

Table 5. Talazoparib Dose Reduction for Toxicity

Talazoparib Dose Level	Talazoparib Dose (mg/day)
Initial maximum dose [1]	**1.0**
First dose reduction	0.75
Second dose reduction	0.50
Third dose reduction	0.25

1. If the starting dose is less than 1.0 mg/day, dose reductions will be in 0.25 mg/day increments.

9.1.2. Assessment of Abnormal Liver Tests

Patients who develop abnormal liver tests (AST, ALT, total bilirubin), abnormal international normalized ratio (INR) values, or signs or symptoms of hepatitis during the study treatment period may meet the criteria for temporarily withholding or permanently discontinuing talazoparib as specified in United States (US) Food and Drug Administration (FDA) Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009). Patients who meet criteria for permanent discontinuation or temporary withholding of talazoparib or who do not meet the criteria but who have abnormal liver tests are to be followed up according to the recommendations in this section.

Talazoparib should be withheld for any liver test abnormality listed in Table 6.

Table 6. Criteria for Temporary Withholding of Talazoparib in Association with Liver Test Abnormalities

Baseline AST or ALT Value	Elevation
≤3 × ULN	>5 × ULN (ALT or AST ≥3 × ULN with the presence of signs and symptoms consistent with acute hepatitis and/or eosinophilia [≥500 eosinophils/μL])
>3 × ULN	>8 × ULN
Baseline Total Bilirubin Value	Elevation
≤1.5 × ULN	>3 × ULN (>5 × ULN in patients with a baseline total bilirubin value of >1.5 × ULN and ≤3 × ULN [patients with Gilbert syndrome or for whom indirect bilirubin concentrations suggest an extrahepatic source of elevation])

For rechallenge, dose modification may be required per Table 3.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Talazoparib should be withheld pending investigation of alternative causes of liver injury (Table 7). When withholding talazoparib, follow-up should continue for possible drug-induced liver injury until the liver test abnormalities resolve to baseline grade. Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values.

Table 7. Criteria for Temporary Withholding of Talazoparib in Association with Liver Test Abnormalities

Recommended tests: Complete blood count with differential to assess for eosinophilia; Serum total immunoglobulin G (IgG), antinuclear antibody (ANA), antismooth muscle antibody, liver kidney microsomal antibody 1 (LKM1), and liver cytosol type 1 antibodies (L-C-1) to assess for autoimmune hepatitis; Serum acetaminophen (paracetamol) concentration.
Obtain a more detailed history: Prior and concurrent diseases or illness; Exposure to environmental and/or industrial chemical agents; Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever; Prior and concurrent use of alcohol, recreational drugs, and special diets; Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms; Obtain viral serologies for hepatitis A, B, C, and E (D if positive for hepatitis B), cytomegalovirus, Epstein-Barr virus, herpes simplex virus.
Recommended tests as clinically indicated: Echocardiogram (ECHO); Serum and urine copper and serum ceruloplasmin; Iron studies (serum iron and ferritin) and transferrin saturation Serology for celiac disease; Serum alpha-1 antitrypsin; Creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear; Appropriate liver imaging; Hepatology consult (liver biopsy may be considered in consultation with a hepatologist).

The investigator and sponsor should discuss and agree with any decision to rechallenge. Following rechallenge, patients should be closely monitored for signs and symptoms of hepatitis and/or abnormal liver test results. If signs or symptoms recur with rechallenge, talazoparib should be permanently discontinued. Rechallenge should never occur if the criteria for permanent discontinuation are clearly met.

9.1.2.1. Criteria for Permanent Discontinuation of Talazoparib in Association with Liver Test Abnormalities

Talazoparib should be discontinued permanently if all of the following 4 criteria are met (ie, potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥3 times ULN (>5 ×ULN if baseline ALT/AST is >3 ×ULN).

2. Total bilirubin increases to >2 times ULN or INR >1.5.

3. Alkaline phosphatase value does not reach 2 times ULN (note: in the presence of elevated alkaline phosphatase associated with bone metastases, gamma glutamyl transferase should be tested and the results should be within the reference range).

4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:

    - Hepatobiliary tract disease;
    - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus);
    - Congestive heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia;
    - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
    - Alcoholic hepatitis;
    - Nonalcoholic steatohepatitis (NASH);
    - Autoimmune hepatitis;
    - Wilson disease and hemochromatosis;
    - Alpha-1 antitrypsin deficiency.

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than those noted above, then it should be determined (based on the patient population as determined by the originating protocol and/or severity of the hepatotoxicity or event) whether talazoparib should be withheld or permanently discontinued as appropriate for the safety of the patient. When talazoparib is temporarily withheld or permanently discontinued due to a potential drug-induced liver injury, a period of close observation is to commence until the liver test abnormalities return to baseline or normal values. The evaluations listed in Table 8 should be performed.

Table 8. Monitoring of Liver Tests for Potential Drug Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]) and INR Tests
After the initial liver test abnormality	Within 24 hours
If AST or ALT ≥3 × ULN (>5 × ULN if baseline ALT/AST is >3 × ULN), and total bilirubin >2 × ULN or INR >1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥3 × ULN (>5 × ULN if baseline ALT/AST is >3 × ULN) and total bilirubin or INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal.

As drug-induced liver injury is a diagnosis of exclusion, it is important to initiate investigation of alternative causes for abnormal liver tests, which may include consultation with a hepatologist. The medical monitor should be contacted for questions regarding adequate follow-up tests.

9.2. Physical Examinations and Vital Signs

The investigator will perform brief physical examinations and vital sign measurements according to the schedule of activities (Appendix 1). Interval medical history will be reviewed as a part of physical examinations.

Brief physical examinations will be symptom-directed, including investigating any new abnormalities, and may include an assessment of systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms.

Vital sign measurements will include blood pressure, heart rate, and temperature. Weight will be measured at the time of the examination.

Clinically significant abnormalities observed after signed informed consent is obtained and before the first dose of talazoparib in this study must be documented on the medical history case report form; any clinically significant change observed after the first dose of talazoparib must be documented as an adverse event.

10. STATISTICAL METHODS

10.1. Statistical and Analytical Plans

10.2. Analysis Populations

The safety population is defined as all patients who receive any amount of talazoparib. The safety population will be used for all safety analyses.

10.3. Safety Analyses

All safety analyses will be performed using the safety population. Drug exposure will be summarized using descriptive statistics. Treatment-emergent safety data will be collected from the first dose of talazoparib through approximately 30 days after the last dose (ie, permanent discontinuation) or before initiation of a new antineoplastic therapy, whichever occurs first as applicable based on the protocol version at the time the patient discontinued. For protocol version 4.0 or later, treatment-emergent safety data will be collected from the first dose of talazoparib through and including 30 days after the last dose (ie, permanent discontinuation) regardless of initiation of a new antineoplastic therapy.

The safety of talazoparib monotherapy will be evaluated by the analysis of incidence of serious and nonserious adverse events; severity of adverse events; incidence of dose reductions and of permanent treatment discontinuation due to adverse events; and incidence of new clinically significant changes in vital signs and clinical laboratory values.

Adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the CTCAE version 4. The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, severity, seriousness, and outcome (eg, leading to permanent treatment discontinuation). Descriptive statistics will be used.

Laboratory values will be classified for severity using the CTCAE, version 4. Laboratory shift tables of baseline to maximum or minimum postbaseline results to each subsequent visit will be produced as appropriate.

Vital signs will be tabulated descriptively when applicable.

11. STUDY COMMITTEES AND COMMUNICATIONS

No formal study committees are planned for this study.

12. LABORATORY REQUIREMENTS

The local laboratory will analyze the clinical laboratory safety samples for this study as described in Section 9.2.

13. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

Before initiating the study, the investigator must provide the following documents to the sponsor:

- Fully executed and signed Form FDA 1572;
- Fully executed clinical trial agreement;
- Current curriculum vitae (also applies to all subinvestigators listed on the Form FDA 1572);
- Financial disclosure (also applies to all subinvestigators listed on the Form FDA 1572);

- Signed protocol signature page;
- Signed acknowledgment of receipt of the current investigator brochure;
- Ethics committee (EC) approval letter;
- EC-approved informed consent form;
- Additional documents as necessary per local requirements.

If an investigator changes during the course of the study, the sponsor and any local regulatory authorities, as applicable, must first approve the change of investigator and the new investigator must provide the sponsor all of the documents listed above.

The sponsor personnel or representatives may visit the study site, if necessary, before initiation of the study to review information with study site personnel about protocol requirements pertaining to the study drug, case report forms, monitoring, serious adverse event reporting, and other relevant information.

13.1. Ethics

13.1.1. Ethics Committee

Before initiating the study, the investigator will obtain confirmation from the EC that the EC is properly constituted and compliant with all requirements and local regulations.

The investigator will provide the EC with all appropriate material, such as the protocol, current investigator brochure, site-specific informed consent form, and other written information provided to the patients. The study will not be initiated until the investigator obtains appropriate EC approval in writing for the protocol and informed consent document, and copies are received by the sponsor.

EC and health authority approval will be obtained for any substantial protocol amendments and informed consent revisions before implementing the changes. The investigator will provide appropriate reports on the progress of the study to the EC, per local requirements, and to the sponsor or designee in accordance with applicable local regulations.

13.1.2. Ethical Conduct of the Study

This study will be conducted under the guiding principles of the World Medical Association Declaration of Helsinki, including current Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an EC; the study will be conducted by scientifically and medically qualified persons; the anticipated benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will provide written informed consent before any protocol-specific tests or evaluations are performed.

13.1.3. Patient Information and Informed Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The 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 shall 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 natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient 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 investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study specific activity is performed. The investigator will retain the original of each patient's signed consent document.

13.1.4. Maintaining Patient Confidentiality

All reports and patient samples will be identified only by the originating study ID number and actual initials (if permitted) or mock initials and date of birth (month/year only if no date is permitted) in order to maintain patient confidentiality. Additional patient confidentiality issues are addressed in the clinical trial agreement and in the informed consent form signed by each study participant.

13.2. Data Quality Assurance

13.2.1. Data Management

Clinical data management will be performed by the sponsor or designee according to procedures described in a comprehensive data management plan. The data management plan will include procedures for processing the data from this study, and will describe the responsibilities of the sponsor and designee when clinical data management is provided by an external vendor. In particular, the data management plan will include a list of the standard operating procedures that apply to this study.

Adverse events and medications will be coded using MedDRA and the World Health Organization Drug Dictionary (WHO-DD), respectively. The dictionary versions will be named in the data management plan.

13.2.2. Case Report Forms

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

13.2.3. Study Monitoring

The sponsor or designee will monitor this study in accordance with current GCP guidelines. By signing this protocol, the investigator grants permission to the sponsor or designee and appropriate regulatory authorities to conduct onsite monitoring of all appropriate study documentation. To ensure the accuracy of data collected on the case report forms, it is mandatory that sponsor representatives (eg, study monitor) have direct access to original source documents (eg, paper or electronic patient records, patient charts, and laboratory reports) needed to verify the entries on case report forms. During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various original medical records (paper or electronic) related to the study. The study monitor will be responsible for inspecting the case report forms at regular intervals throughout the study, to verify the adherence to the protocol and the completeness and correctness of all case report form entries. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2.4. Study Audits

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed upon time. By signing this protocol, the investigator grants permission to the sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

13.3. Investigational Product Accountability

The investigator must maintain accurate records of all study drug supplies received. All records must be made available to the sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH GCP guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the sponsor's drug accountability log or other sponsor-approved pharmacy log;
- That study drug is handled and stored safely and properly in accordance with the label and the study protocol;
- That study drug is only administered or dispensed to study patients in accordance with the protocol;
- That any used or unused drug is returned by the patient at each required visit;

- That any unused study drug is returned to the sponsor-designated facility or standard procedures for the alternative disposition of unused study drug are followed and only after approval by the sponsor representative.

Drug inventory and accountability records for the study drug will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drug to any persons except the patients in this study;

- The investigator/pharmacist will keep the study drug in a pharmacy or other locked and secure storage facility under controlled storage conditions as required by the study drug label, accessible only to those authorized by the investigator to dispense the study drug;

- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient;

- The investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record at the conclusion or termination of this study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible;

- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the sponsor agrees with the procedure, and after drug accountability has been conducted by the sponsor or representative, unless otherwise approved. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the sponsor or designee upon request for review and approval before the first onsite destruction. Unused study drug not destroyed at the site must be returned to the sponsor-designated facility at the end of the study or upon expiration.

13.4. Compensation, Insurance, and Indemnity

In the event of a side effect or injury, appropriate medical care as determined by the investigator or designated alternate will be provided.

If bodily injury is sustained, resulting directly from the use of the study drug or by required study procedures, the sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the patient's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the study doctor and study staff. No other compensation of any type will be provided by the sponsor. Financial compensation for lost wages, disability, or discomfort due to the study participation or procedures is not available.

13.5. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

Investigators must maintain all study documentation for at least 2 years following the approval of the drug, or until 2 years after the investigational drug program is discontinued, or longer if required by local regulations. Study documentation includes all essential documents as defined in ICH E6 Guidelines for Good Clinical Practice. The sponsor or designee will notify the investigator when any records may be discarded, but investigators must comply with local regulations.

13.6. Study Termination

The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary. Pfizer retains the right to discontinue development of talazoparib at any time.

The sponsor reserves the right to terminate the study anytime. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drug, as well as other important information that may affect proper conduct of the clinical study, the sponsor may terminate the study and send a written notice of the termination along with the reasons to the investigator.

If an investigator or the investigator’s EC intends to terminate participation in the study, the investigator must immediately inform the sponsor and provide the reason for it.

14. USE OF STUDY INFORMATION AND PUBLICATION

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of Pfizer (sponsor), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsor and are confidential. Written approval from the sponsor is required before disclosing any information related to this clinical trial, and no publications initiated by investigators may be published until all protocol-defined primary and secondary endpoints are published in a manuscript. Every attempt will be made to minimize the interval between the completion of data analysis and publication of the study results. Recommendations for the timing of presentation of trial endpoint data and the publication venues (congresses/journals) will be given by the sponsor's Publications Subcommittee.

Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

In accord with standard editorial and ethical practice, the sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data.

In this case, a coordinating investigator and lead author will be designated by mutual agreement.

Any formal publication of the study in which input of sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate sponsor personnel. Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts or stricter local criteria (ICMJE, 2015). The sponsor does not compensate for authorship of a publication and all authors will be required to disclose, as part of the publication submission, any potential conflicts of interest, including pertinent financial or personal relationships with the sponsor or related entities, including sponsors of competing products that might be perceived to be a source of bias. Authorship is decided on an individual basis and the sponsor's Publications Steering Committee and sponsor representatives will mutually determine authors and their sequence on individual publications based on the relative contribution of each author to the study and/or publication.

Investigators in this study agree to have their name listed as an investigator in any publication reporting results from this study, whether or not they are an author on the publication.

Professional medical writing support is permissible, and any writing support will be acknowledged in each applicable publication, explaining the role the professional writer had in the drafting of the publication. Medical writing and publications support funded by the sponsor on behalf of investigator authors will be considered as a transfer of value under the reporting requirements of Section 6002 of the Patient Protection Affordable Care Act (PPACA, 2010). Transfer of value will be allocated to authors following sponsor guidelines.

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16. INVESTIGATOR SIGNATURE

PFIZER, INC.

A Single-Arm, Open-Label, Multicenter, Extended Treatment, Safety Study in Patients Treated With Talazoparib

Signature of Agreement for Protocol MDV3800-13 (C3441010) Amendment 4 –14 Nov 2018

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practice and the Declaration of Helsinki, and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312.

Print Study Site Name	Study Site Number
Print Investigator Name	
Investigator Signature	Date

Appendix 1. Study Schedule of Activities

Study Period or Visit[1]	Treatment							Unsched[2]	Safety FU[3]
Study Week Interval	1[4]	3	5	7	9	Through Week 25	After Week 25[5]	Varies	Varies
Study Week	1	3	5	7	9	13, 17, 21, 25	Every 8 Weeks	Varies	Varies
Window (Days)[6]	-28	±7	±7	±7	±7	±7	±7	Not Applicable	-3 to +10
Informed consent[7]	X								
Eligibility criteria[7]	X								
Brief physical examination[8]	X		X		X	X	X	X	X
Vital signs[9]	X		X		X	X	X	X	X
Adverse events review[10]	X		X		X	X	X	X	X
Con medications review	X		X		X	X	X	X	X
Dispense talazoparib[11]	X (day 1)		X		X	X	X		
Talazoparib accountability			X		X	X	X	X (optional)	X
Local clinical lab eval[12]	X		X		X	X	X	X (optional)	X
CBC only[13]		X		X			X (q4 weeks)		
Pregnancy test[14]	X		X		X	X	X (q4 weeks)	X (optional)	X
Blood sample for storage[15]	X								

1. Patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study eg, if a PRP-001 patient is on an every 4 week schedule in the originating study, the patient is required to complete the week 5 and week 9 visits but not the CBC assessments at week 3 and week 7; afterwards, these patients would follow the schedule of activities as above.
2. Anytime necessary to assess or follow up adverse events, for dose modification, or as requested by patient or investigator.
3. Approximately 30 days after the last dose of talazoparib. Phone patients for adverse event follow up if they do not come to the clinic.
4. First dose will occur within 2 months after the last dose in the originating study.
5. Adjust schedule as clinically indicated.
6. Drug supply must be taken into account if a window is used to schedule the next visit. Visit procedures may be split across the window to allow for drug resupply and completion of study procedures.
7. Obtain informed consent before performing any study-specific procedures. Ensure consent is on the current version of form approved by the ethics committee. May be completed while the patient is participating in the originating study and may be completed greater than 28 days prior to the week 1 visit.
8. Symptom-directed, including investigating any new abnormalities, and may include an assessment of systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal) per standard of care at the study site or as clinically indicated by symptoms.
9. Vital signs include blood pressure, heart rate, and temperature. Measure in the supine position. Measure weight.

10. Collect serious adverse event information from the time of signed informed consent through through and including 30 days after the last dose of talazoparib. As noted above, AEs including SAEs for all enrolled patients that occur between consent for this study and first dose in the study are to be recorded on the Medical History CRF and not as AEs. AEs are recorded in the qualifying originating study as AEs, if occurring during the active collection period of the qualifying originating study.
11. Dispense 4- or 8-week supply after completing all other activities/assessments for the visit. First dose is taken in clinic on day 1; record time of dose.
12. Hematology (including CBC testing), serum chemistry per Table 3. Review clinical laboratory results before dosing at each visit. Investigators must report any clinically significant abnormalities as adverse events per CTCAE v4 criteria. If abnormal, refer to Section 9.1.1.
13. Perform CBC testing only every 2 weeks through week 9 and every 4 weeks thereafter ; if abnormal, refer to Section 9.1.1.
14. For women of childbearing potential. Perform a serum pregnancy test before the first dose and a urine or serum test every 4 weeks thereafter before dosing. Discontinue talazoparib if a pregnancy test is positive.
15. For patients who did not have a sample collected prior to dosing in the originating study for possible reflex testing for HBV (HBsAg, anti-HBc) and HCV (HCV antibody, reflex testing for HCV RNA if positive) or who were not tested for hepatitis: collect blood sample to be stored locally. May be completed while the patient is participating in the originating study.

Anti-HBc, hepatitis B core antibody; CBC, complete blood count; con, concomitant; CTCAE v4, Common Terminology Criteria for Adverse Events, version 4; eval, evaluation; FU, follow-up; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; lab, laboratory; q, every; unsched, unscheduled.

Appendix 2. France Appendix

This appendix applies to study sites located in France.

1. GCP Training.

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product.

No subjects or third-party payers will be charged for investigational product.

3. Inspections.

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.

4. Urgent Safety Measures.

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

5. SUSARs.

Pursuant to a sponsor's safety reporting obligations under 21 CFR 312.32(c)(1), Pfizer will report to the Investigator all Serious Unexpected Suspected Adverse Reactions ("SUSARs"). Investigator will receive and review SUSAR reports and report SUSARs to the responsible IRB/IEC according to institution's guidelines. Institution will retain SUSAR reports.