TALAPRO-1: A PHASE 2, OPEN-LABEL, RESPONSE RATE STUDY OF TALAZOPARIB IN MEN WITH DNA REPAIR DEFECTS AND METASTATIC CASTRATION-RESISTANT PROSTATE CANCER WHO PREVIOUSLY RECEIVED TAXANE-BASED CHEMOTHERAPY AND PROGRESSED ON AT LEAST 1 NOVEL HORMONAL AGENT (ENZALUTAMIDE AND/OR ABIRATERONE ACETATE/PREDNISONE)

Investigational Product Number:	PF-06944076
Investigational Product Name:	Talazoparib
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Phase:	2a

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment #4	15-Nov-2018	Rationale: The primary purpose of Protocol Amendment 4 is to address updated information reported in the August 2018 version of the Talazoparib Investigator's Brochure. In addition, guidance for talazoparib dose modifications due to adverse events was updated to align with the Risk Management Committee (RMC) recommendations and the proposed regional labels. Changes included: • Extension of the time required, for contraceptive use and for patients to refrain from sperm donation, from 105 days to 4 months. • Clarification/changes regarding prior and concomitant medications. • Clarifications to responses to adverse events, including talazoparib dose modifications. • Updated safety and efficacy data from clinical studies in patients that have taken talazoparib. • Updated pharmacokinetics data. • Update to the benefits and risks assessment. • The section pertaining to medication errors was updated to address talazoparib overdose. In addition, the following major changes were made: • References to the protocol number were updated to reflect the change in sponsorship from Medivation to Pfizer. • Given that the protocol is following a modified RECIST1.1./PCWG3 criteria to assess ORR, time to response, radiographic PFS, and duration of response, the term "modified RECIST1.1/PCWG3" has been introduced in the protocol.

		• Addition of secondary endpoint measure: "Proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline". • Clarification to indicate that patients enrolled in prior versions of the protocol, regardless of the type of DDR mutation or presence of measurable disease, will follow the same schedule of activities and discontinuation criteria as described in the current version of the protocol. • Clarification to indicate that for prior historical data reporting DDR+ mutation that may be considered for patient eligibility, if sufficient residual DNA is available at Foundation Medicine, this could be used to confirm eligibility, noting that if eligibility for enrollment is established based either on prior results or residual DNA testing, available archival or de novo tumor tissue also should be submitted prior to Day 1. • The name of the Foundation Medicine test used to determine DDR positivity is now noted as FoundationOne CDx™ (formerly, FoundationOne®). • Clarification that central laboratory safety assessments are to be done at every scheduled visit, as well as unplanned, at the investigator's discretion, or to monitor adverse events or decide dosing modifications, noting that local safety lab assessments may also be performed but should not replace central assessments. All data from local labs are to be entered in the appropriate CRF. • Clarification regarding PSA collection. • Clarification regarding assessment of radiographic imaging with details added to the criteria to document disease progression.

		• Adverse Event (AE) and Serious Adverse Event (SAE):
		  • Noted that AEs and SAEs will be followed until respective event or its sequelae resolves or stabilizes to a level acceptable to the investigator and the sponsor concurs with that assessment.
		  • Clarified the timeframe to record research related injuries.
		• Data Analysis/Statistical Methods:
		  • Definition of the DDR Deficient Measurable Disease population; removal of ITT population.
		  • Updates include additional details regarding study secondary efficacy analyses, interim analysis and sample size definition.
		• Data Handling and Record Keeping:
		  • To address data protection, included text that describes measures to be taken to ensure protection of personal data.
		• Added to the Reference section:
		  • Litton JK et al, Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018 Aug 3;379(8):753-763.
		  • Lorente D et al, Circulating tumour cell increase as a biomarker of disease progression in metastatic castration-resistant prostate cancer patients with low baseline CTC counts. Ann Oncol. 2018 Jul 1;29(7):1554-1560.
		  • Modified Appendix 6. Country Specific Amendment: France. Dose modification tables for France (Table 8: Dose Modification due to an Adverse Event and Table 9: Criteria For Temporary

		Withholding of Study Drug in Association with Liver Test Abnormalities) were removed given that for Amendment 4, the dose modification guidance was updated to align as per RMC recommendations and proposed regional labels. • Added Appendix 7 to address a request from the German Ethics Committee regarding the enrollment in clinical studies of persons who have been housed in an institution following a regulatory or judicial order. Additional changes were administrative or minor clarifications/corrections.
Amendment #3	15-Feb-2018	Administrative changes/clarifications: Rationale- The protocol has been updated with the following administrative changes/clarifications: A clarification was added to the footnote for Table 2, and in Section 6.2.3, indicating that the peripheral blood sample should be submitted only if the sample was not already submitted at prescreening. Table 3, footnote 1 and Section 6.3.3: a clarification was added stating that unplanned sample collection or assessments can be done to account for any insufficient, inadequate, or missed sample or assessments. Table 3, noted an unscheduled PK collection. The following typographical errors were corrected: In Section 5.10, Table 12 (as in Table 12. Instructions for Use of Concomitant Therapies) should be listed instead of Table 4. In Section 6.3.2, the word electronic was included in error. In Section 6.3.3, Table 3 (referring to Unscheduled Visit Procedures) should be listed instead of Table 13.

		In Section 7.1.2, Table 14 (as in Table 14. Confirmatory Imaging Requirements for Soft Tissue per RECIST 1.1 and Bone per PCWG3) should be listed, not Table 13. In Section 7.5, removed Table 4. In Section 8.1.3 changed "Patient Withdrawal" to "Permanent Treatment Discontinuation" In Section 8.4.4, removed 'Lack of Efficacy' since this study is not testing a marketed product. In Section 9.8, Tables 17 and 18 (as in Table 17. Response Rates and Exact 95% CI for 60 Patients; Table 18. Response Rates and Exact 95% CI for 100 Patients) should be noted, not Table 1 and Table 2. Added to the Reference section: Brookmeyer R, Crowley JJ. A confidence interval for median survival time. Biometrics. 1982 Mar; 38(1):29-41.
Amendment #2	20-Dec-2017	Rationale: The protocol has been updated with the following: Major changes included the following: • Amended to include a minimum of 100 patients with measurable soft tissue disease and DNA damage repair (DDR) deficiencies (as assessed using a panel of 13 genes where deficiency is likely to sensitize to poly (ADP-ribose) polymerase (PARP) inhibitor therapy); • Eliminated Cohort B, a cohort that had included subjects with DDR deficiencies assessed using an expanded DDR gene panel of genes where deficiency may sensitize to PARP inhibitor therapy. The cohort was eliminated given that not enough patients with rarer DDR mutations would have been projected to be enrolled to permit robust assessment of Overall Objective Response rates for those rarer genes.

		Addition of secondary endpoint measures:
		
		• Proportion of patients with a CTC count of 1 or more (detectable) per 7.5 mL of blood at study entry that decreased to CTC=0 (undetectable) per 7.5 mL of blood anytime on study;
		
		• PRO Analyses (1) Time to deterioration of pain will be measured. (2)Longitudinal mixed effect-model analyses to assess change from baseline in pain symptoms and general health status.
		
		CCI [redacted]
		
		Removal of ctRNA analysis.
		
		Inclusion/Exclusion Criteria were modified:
		
		• Patients must have measurable soft tissue disease per RECIST1.1;
		
		• Allows historical Foundation Medicine tissue biopsy data (with sponsor approval) to be included for eligibility assessment;
		
		• Patients whose only evidence of metastasis is measurable soft tissue disease below the aortic bifurcation will be acceptable. Neither bone metastases on bone scan nor non-measurable soft tissue disease alone will qualify a patient.
		
		• Modified the exclusion criteria regarding:
		
		  • Prior platinum-based chemotherapy;
		
		  • Treatment with any cytotoxic or investigational drug(s) before and/or during study participation;
		
		  • Entry threshold for albumin.

		Adverse event reporting: • Updated to align with the current Pfizer protocol template including safety template language; for prescreening, added text regarding research-related injury and clarification regarding AE reporting; • Following amendment 2 approval, investigators need not report overdose as an SAE if there is no accompanying sign or symptom meeting the definition of SAE. Study Procedure: • Data base recording of local lab PSA measurements; • Clarified that talazoparib dose may not exceed 0.75 mg for patients with moderate renal impairment. Data Analysis: • Intent-to-treat (ITT) population is defined as all enrolled patients who receive any amount of study drug and have measurable soft tissue disease. Additional changes were administrative and required as per the Pfizer protocol template.
Amendment #1	31-Mar-2017	The protocol was updated with the following major changes: • No longer require that all patients with CRPC to enroll with measurable disease at screening (per RECIST 1.1). • [redacted] • Added analyses of best overall response rate, time to objective response, duration of response, and radiographic progression free survival (PFS) based on investigator assessment to allow comparison with central review assessment.

		[redacted]  Increased the frequency of clinical laboratory tests after week 25 from every 12 weeks to every 8 weeks for increased patient safety and consistency across talazoparib studies. Clarified that the sponsor will obtain approval from the appropriate regulatory authority for any substantial amendments to the protocol prior to implementation. • Added results of a talazoparib embryo-fetal development study in rats. • Added guidance for dose modification of talazoparib and updates talazoparib product information for increased patient safety and consistency across talazoparib studies. Additional changes were administrative or minor corrections.
Original protocol	01-Jun-2016	N/A

These amendments incorporate all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Overview

Talazoparib (also known as PF-06944076, MDV3800) is being investigated for the treatment of metastatic castration-resistant prostate cancer (mCRPC) with DNA damage repair deficiencies in men whose disease has previously progressed on novel hormonal therapy (NHT: enzalutamide and/or abiraterone acetate) for the treatment of mCRPC and who were previously treated with taxane-based chemotherapy for metastatic disease.

Background and Rationale

Castration-resistant prostate cancer represents a lethal transition in the progression of prostate cancer, with most patients ultimately succumbing to the disease. Prior to the recent approval of novel hormonal therapies (NHT) (enzalutamide, abiraterone acetate/prednisone), the only approved therapies for metastatic CRPC were docetaxel, cabazitaxel and sipeleucel-T. The approval of NHTs in metastatic CRPC previously treated with docetaxel (De Bono et al, 2011; Scher et al, 2012) represented a therapeutic advance for these patients.

Poly (adenosine diphosphate [ADP]-ribose) polymerase 1 (PARP1) and PARP2 play important roles in DNA repair (Schreiber et al, 2006; Curtin, 2005). Inhibition of PARP catalytic activity results in synthetic lethality whereby persistent single-strand DNA breaks lead to irreparable double-strand DNA breaks in cells with defective homologous recombination mechanisms. Moreover, PARP inhibitors also trap the PARP enzyme on DNA to a variable extent, including that of tumor cells, thereby preventing DNA replication and transcription. Talazoparib is a potent, orally bioavailable, small molecule PARP inhibitor in development for the treatment of a variety of human cancers. Single-agent treatment with talazoparib demonstrates potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA-damaging chemotherapy. Talazoparib in preclinical models demonstrates potent cytotoxic effects from PARP trapping.

Proof of concept that a PARP inhibitor may treat advanced metastatic CRPC with DNA damage repair deficiency was established in a Phase 2 study (TOPARP-A) with olaparib, which enrolled men heavily pre-treated with taxane-based chemotherapy and NHT (Mateo et al, 2015). Thus, the current study was designed given the results of TOPARP-A for the treatment of late stage metastatic CRPC for which there are no approved treatments tested in the target population of this study.

Objectives

Primary Objective:

- To evaluate the efficacy of single agent talazoparib in DNA damage repair (DDR) + metastatic CRPC, as measured by best objective response rate (ORR).

Secondary Objectives:

- To evaluate efficacy with respect to the following parameters:
  - Time to objective response;
  - Duration of response;
  - Proportion of patients with prostate-specific antigen (PSA) decrease ≥50%;
  - Proportion of patients with conversion of circulating tumor cell (CTC) count;
  - Time to PSA progression;
  - Radiographic progression-free survival (PFS);
  - Overall survival.
- To evaluate the safety of talazoparib in this patient population.
- To evaluate the following patient-reported outcomes:
  - Time to deterioration in pain as assessed by the Brief Pain Inventory Short Form (BPI-SF);
  - Change from baseline in pain per BPI-SF;
  - Change from baseline in general health status as assessed by the European Quality of Life 5-Domain 5-Level Scale (EQ-5D-5L).
- To evaluate the pharmacokinetics (PK) of talazoparib.

CCI [redacted]

STUDY DESIGN

This is an international, phase 2, open-label, soft tissue response rate study of talazoparib (also known as PF-06944076, MDV3800, BMN 673), a poly (ADP-ribose) polymerase (PARP) inhibitor in development for treatment of cancer. PARP inhibition has been shown to produce clinical responses in metastatic castration-resistant prostate cancer (mCRPC), particularly in patients with DNA damage repair deficiencies. PARP inhibitors are thought to induce cell toxicity by inhibiting PARP catalytic activity as well as by trapping PARP-DNA complexes, which prevent DNA repair, replication, and transcription.

Nonclinical studies have shown that talazoparib has potent cytotoxic effects via both mechanisms, with greater cell toxicity from PARP trapping. In this study, a minimum of 100 men with measurable soft tissue disease and progressive metastatic CRPC with DNA damage repair deficiencies likely to sensitize to PARP inhibition will be studied. Patients will be evaluated for genomic deficiencies in DNA damage repair genes as assessed by a gene mutation biomarker panel where relevant mutations are likely to sensitize to PARP inhibition.

Eligible patients must have previously received 1 to 2 chemotherapy regimens including at least 1 taxane-based regimen for treatment of metastatic prostate cancer, and progressed on at least 1 line of novel hormonal therapy (enzalutamide and/or abiraterone acetate/prednisone) for treatment of metastatic CRPC. Patients will be evaluated at prescreening (optional) or screening for DNA damage repair deficiencies as assessed by a gene mutation biomarker panel. Approximately 100 patients with DNA damage repair deficiencies as assessed by a panel of genes likely to sensitize to PARP inhibition will be enrolled.

Newly enrolled patients will have measurable soft tissue disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Patients must consent to submit sufficient tumor tissue (de novo tumor biopsy or archival tissue) to be centrally assessed for mutations in selected genes associated with DNA damage repair (DDR) deficiencies using the FoundationOne CDx™ (Foundation Medicine) panel. Previous identification of DNA repair deficiencies likely to sensitize to PARP inhibition, may be considered with sponsor approval. CCI

Patients enrolled in prior versions of the protocol, regardless of the type of DDR mutation or the presence of measurable disease, will follow the same schedule of activities and discontinuation criteria as described in the current amendment.

Study periods include prescreening (optional), screening, treatment, safety follow-up, and long-term follow-up. Safety follow-up after permanent discontinuation of study drug treatment will occur approximately 28 days after the last dose of study drug or before initiation of a new antineoplastic or investigational therapy, whichever occurs first. Long-term follow-up will occur (usually every 8-12 weeks) after safety follow-up. Radiographic imaging should continue during long-term follow-up for patients who discontinue study drug for any reason other than radiographic progression determined by independent central review, withdrawal of consent for follow-up, or death.

Study Treatments

Patients will receive talazoparib, 1 mg daily by mouth, with continued androgen deprivation (gonadotropin-releasing hormone [GnRH] therapy or bilateral orchiectomy). Talazoparib will be administered until radiographic progression is determined by independent central review, or unacceptable toxicity, or withdrawal of consent, or death. In addition, talazoparib can continue to be administered upon disease progression only if, in the opinion of the investigator the patient is clinically benefitting, no new concurrent systemic therapy is

started, and the sponsor is notified. For patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30-59 mL/min/1.73 m^2 as per central laboratory) at screening, the starting dose will be 0.75 mg/day. Study drug should not be discontinued based solely on PSA or CTC count increases.

Statistical Methods

The primary objective of the study is to evaluate the efficacy of single agent talazoparib in DDR+ mCRPC, as measured by best objective response rate (ORR). An objective response is defined as a best overall response of complete response (CR) or partial response (PR) per RECIST 1.1. Response must be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated computed tomography (CT) or magnetic resonance imaging (MRI) and with no evidence of confirmed bone disease progression per Prostate Cancer Working Group 3 (PCWG3) criteria on repeat bone scan at least 6 weeks later by independent central review.

Efficacy Analyses

The statistical methods and analyses for this study will be described in detail in the statistical analysis plan.

DDR Deficient Measurable Disease population is defined as all enrolled patients who have measurable soft tissue disease at screening by independent central review (ICR), have DDR deficiencies likely to sensitize to PARP inhibitor therapy and receive at least one dose of talazoparib. The DDR Deficient Measurable Disease population will be used for all baseline characteristics summaries and efficacy analyses.

Three analyses are planned, including an initial safety/efficacy analysis followed by two efficacy analyses. The initial safety/efficacy analysis will be performed after 20 patients with measurable soft tissue disease and DDR deficiencies likely to sensitize to PARP inhibitor therapy have received the study drug for at least 8 weeks. Efficacy analyses of the primary endpoint will also be performed when 60 and 100 patients have complete at least 6 months of study treatment or are no longer being followed (ie, have withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up). All safety analyses will be performed using the safety population, defined as all patients who receive any amount of study drug.

Summaries and listings of efficacy and baseline data for patients that were enrolled under previous protocol versions and who are not part of the DDR Deficient Measurable Disease population will be described in the statistical analysis plan.

All patient-reported outcome (PRO) analyses will be conducted on the PRO population, defined as all patients from the DDR Deficient Measurable Disease population who have completed a baseline and at least one post-baseline PRO assessment prior to the end of study treatment.

The PK population is defined as all patients from the safety analysis set who have at least 1 reportable drug concentration data point. The CTC evaluable population is defined as all patients with a baseline CTC assessment and at least 1 postbaseline CTC assessment from the DDR Deficient Measurable Disease population. CCI [redacted]

Primary Efficacy Endpoint:

- Best ORR: The proportion of patients with a best overall soft tissue response of CR or PR per RECIST 1.1 by independent central review. Soft tissue responses must be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated CT or MRI with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria by independent central review.

Secondary Efficacy Endpoints:

- Time to objective response: The time from first dose of talazoparib to the first objective evidence of soft tissue response with no evidence of confirmed bone disease progression on bone scan per PCWG3. Soft tissue response is defined as a best overall response of CR or PR per RECIST 1.1 by independent central review. The response must be confirmed at least 4 weeks later with a repeated CT/MRI.

- Duration of response: The time from the first objective evidence of soft tissue response (subsequently confirmed) per RECIST 1.1 by independent central review and no evidence of confirmed bone disease progression per PCWG3 to the first subsequent objective evidence of radiographic progression or death due to any cause, whichever occurs first. Radiographic progression is defined as soft tissue progression per RECIST 1.1 by independent central review or bone disease progression per PCWG3 by independent central review.

- Proportion of patients with PSA response ≥50%: The proportion of patients with confirmed PSA decline ≥50% compared to baseline.

- Proportion of patients with conversion of CTC count: The proportion of patients with a CTC count ≥5 CTC per 7.5 mL of blood at study entry that decreases to <5 CTC per 7.5 mL of blood any time on study.

- Proportion of patients with a CTC count of 1 or more (detectable) per 7.5 mL of blood at study entry that decreases to CTC=0 (undetectable) per 7.5 mL of blood any time on study (Scher et al, 2017).

- Proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline (Lorente et al, 2018).

- Time to PSA progression: The time from first dose of talazoparib to the date that a ≥25% increase in PSA with an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline) is documented, confirmed by a second consecutive PSA value obtained ≥3 weeks (21 days) later.

- Radiographic PFS: The time from first dose of talazoparib to radiographic progression in soft tissue per RECIST 1.1 by independent central review, in bone per PCWG3 by independent central review, or death due to any cause, whichever occurs first.

- Overall survival: Defined as the time from first dose of talazoparib to death due to any cause.

Analyses of best ORR, time to objective response, duration of response, and radiographic PFS will also be evaluated based on assessment by the investigator. The statistical methods and analyses are described in detail in the statistical analysis plan.

PRO Analyses

- Time to deterioration of pain (≥2-point increase from baseline, using question 3 of the BPI-SF), will be measured. In order to adequately measure pain, it is equally important to adequately track analgesic use to ensure that the pain palliation observed is not the result of an increase in analgesic use but rather the effect of the antitumor treatment being studied. After Day 1, pain and analgesic assessments will be completed for each of 7 consecutive days before study visits; pain score averages during the period of reporting will be calculated. Analgesic data (from the analgesic log) will be mapped to the World Health Organization (WHO) analgesic usage score and used concurrently to define pain progression with the BPI SF (Basch E et al, 2013).

- Longitudinal mixed effect-model analyses will be used to assess change from baseline in patient reported pain (assessed by BPI-SF) and general health status (assessed by EQ-5D-5L).

PK Analyses

PK data collections will include predose sampling at Day 1 (baseline sample, drawn prior to patient's taking his first dose of talazoparib) and predose samples at weeks 5, 9, and 13, and postdose sampling at Day 1 and week 5. PK data analyses will include descriptive summary statistics of the predose trough and postdose plasma concentrations for talazoparib by study visit. In addition, the PK data from this study may be used to develop a population PK model. CCI [redacted]

Safety Analyses

The safety of talazoparib will be evaluated by analysis of the incidence of serious and nonserious adverse events, severity of adverse events, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs. Treatment-emergent safety data will be collected from the first dose of study drug treatment through 28 days after the last dose (ie, permanent discontinuation) of study drug or before initiation of new antineoplastic or investigational therapy, whichever occurs first. 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 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used. Laboratory values will be classified by severity using the CTCAE. Laboratory shift tables of baseline to maximum post baseline results to each subsequent visit will be produced as appropriate.

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[redacted]

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Table 1. Study Schedule of Activities: Prescreening (Optional)

General Activities	Comments
	Prescreening may be performed any time before consent is signed for the screening period.
Prescreening informed consent	Use the prescreening consent form. Obtain consent any time before performing any prescreening procedures.
Screening number	Obtain screening number from the interactive response technology (IRT) system.
Adverse Event (AE) and research related injuries	Record in the Case Report Form (CRF) as described in Section 8.4.5.
Pretreatment adverse events review	Refer to Section 8.4.5 for guidance on the reporting of adverse events or research-related injuries during the prescreening phase of the study.
For all patients: Submit fresh or adequate archival tumor tissue. Alternatively, prior results from Foundation Medicine may be considered for eligibility with sponsor approval. If patient genomically qualifies based on prior tumor testing submit adequate archival or fresh tissue if available.	Submit tissue from a de novo biopsy of a safely accessible tumor lesion, or archival tumor tissue, for prospective central laboratory enrollment testing. Test results from prior tumor testing identifying DNA repair deficiencies likely to sensitize to PARP inhibition may be considered for eligibility. If sufficient residual DNA is available at Foundation Medicine this could be used to confirm a patient's eligibility for enrollment. Note that if eligibility for enrollment is established based on either prior results or residual DNA testing, available archival or de novo tumor tissue also should be submitted prior to Day 1 to support concordance analyses and additional molecular profiling, unless prohibited by local regulations or ethics committee (EC) decision. Note: biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel may not be performed for the sole purpose of determining study eligibility.
Demographics Prior Anti-Cancer Therapies Medical History- Prostate Cancer	For all patients, including those who by central laboratory assessment are not found to be genomically eligible: • Obtain patient demographics using the Patient Demographics screening CRF; • Obtain patient prior cancer treatment history using the Prior Cancer Therapy CRF; • Obtain patient prior medical history for prostate cancer using the Medical Prostate History CRF.
CCI [redacted]	[redacted]

Table 2. Study Schedule of Activities: Screening

Study Day	Window	Comments
General Activities		Screening activities may be repeated any time during the screening period if clinically indicated.
Informed consent		Informed consent may be obtained greater than 28 days before Day 1/enrollment; however consent must be obtained before performing any study-specific procedures. Ensure the consent (signed and dated) is the current version of the form approved by the ethics committee and sponsor.
Screening number		Obtain screening number from the IRT system after informed consent is signed, if not obtained at pre-screening.
Demographics;* Prior Therapy;* Medical History*	-28 to -1	Demographics; Prior Anti-Cancer Therapies; Medical History- Prostate Cancer.
Eligibility criteria	-28 to -1	
Enrollment authorization form	-28 to -1	Complete, sign, and fax or email the form with requested items to sponsor or designee at least 2 business days before enrollment (day 1). Patient may proceed to day 1 when sponsor or designee approves by signed form or email correspondence.
12-Lead electrocardiogram	-28 to -1	Local.
Vital signs	-28 to -1	Measure blood pressure, heart rate, and temperature.
ECOG performance status	-28 to -1	Eastern Cooperative Oncology Group.
Physical examination, weight, height	-28 to -1	Assess systems (eg, general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, neurologic, and skeletal).
Pretreatment adverse events review	-28 to -1	Report serious and nonserious adverse event information from time of signed informed consent.
Prior and concomitant medications	-28 to -1	
Submit fresh or adequate archival tumor tissue. Alternatively, prior results from Foundation Medicine may be considered for eligibility with sponsor approval. If patient genomically qualifies based on prior tumor testing, submit adequate archival or fresh tissue if available.	Any time before -1 (Refer to Table 1)	If not obtained at the prescreening visit: submit tissue from a de novo biopsy of a safely accessible tumor lesion, or archival tumor tissue, for prospective central laboratory enrollment testing, Test results from prior tumor testing identifying DNA repair deficiencies likely to sensitize to PARP inhibition may be considered for eligibility. If sufficient residual DNA is available at Foundation Medicine this could be used to confirm a patient's eligibility for enrollment. Note that if eligibility for enrollment is established based on either prior results or residual DNA testing, available archival or de novo tumor tissue also should be submitted prior to Day 1, to support concordance analyses and additional molecular profiling, unless prohibited by local regulations or ethics committee (EC) decision. Note: biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel may not be performed for the sole purpose of determining study eligibility.
CCI [redacted]		[redacted]

Laboratory Evaluations		Refer to the central laboratory instruction manual for sample processing and for estimated turnaround time for results. All laboratory evaluations will be tested centrally except where noted.
Serum chemistry, hematology	-28 to -1	
Testosterone, PSA	-28 to -1	Up to 2 or 3 local prostate-specific antigen measurements (PSA) will be used to determine eligibility, including local PSA values that may have been obtained prior to the patient signing the study ICD and greater than 28 days before Day 1. PSA measurements must be consecutive and at least 1 week apart. The third PSA may, or may not, be the central lab screening PSA. If the screening central lab PSA is lower than local lab PSA #2, then a third local lab PSA may be submitted instead. A central PSA assessment will be done at screening for all patients. Screening PSA (as per central laboratory) must be ≥2 ng/mL for patients qualifying based only on PSA progression. Refer to Section 7.2.1.
Radiographic Assessments		May use scans obtained as part of standard of care before consent was signed and within 42 days before day 1 if scans were performed per the specific study requirements (per imaging manual).
CT of chest; CT or MRI of abdomen and pelvis	-42 to -1	Computed tomography or magnetic resonance imaging.
Whole-body radionuclide bone scan	-42 to -1	

* *Demographics, Prior Anti-Cancer Therapies and Medical History- Prostate Cancer will not be required for patients that have these data recorded at the prescreening visit.*

Table 3. Study Schedule of Activities: Treatment*

Study Period or Visit	**Treatment**									**Unsched[1]**	**Safety FU[2]**
Study Week	**1****	**3**	**5**	**7**	**9**	**13**	**17**	**21**	**25+[3]**	**Varies**	**Varies**
Window (Days)[4]	**na**	**±3 (±7 for scans)**								**na**	**-3 to +10**
Enrollment ID number	X										
General Activities											
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X
Physical exam, weight[6]	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X
BPI-SF, EQ-5D-5L[7]	X	X	X	X	X	X	X	X	X	X	X
Pain Log[19]		X	X	X	X	X	X	X	X	X	X
Analgesic Log[20]		X	X	X	X	X	X	X	X	X	X
Adverse events review[8]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensing[9]	X[7]		X		X	X	X	X	X	X (optional)	
Study drug accountability			X		X	X	X	X	X	X (optional)	
Central Lab Evaluations[10]											
Serum chemistry, hematology[3][11]	X	X	X	X	X	X	X	X	X	X	X
Prostate-specific antigen[21]	X				X	X	X	X	X	X	X
Blood sample for PK[12]	X		X		X	X				X	

Table 3. Study Schedule of Activities: Treatment*

Study Period or Visit	Treatment									Unsched[1]	Safety FU[2]
Study Week	1**	3	5	7	9	13	17	21	25+[3]	Varies	Varies
Window (Days)[4]	na	±3 (±7 for scans)								na	-3 to +10
Blood sample for CTC enumeration[13]	X				X		X		X		X
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Blood sample to be stored for reflex testing for viral hepatitis	X										
Contraception check[22]	X	X	X	X	X	X	X	X	X		X
Radiographic Assessments[18]											
CT of chest, CT or MRI of abdomen and pelvis					X		X		X	X[1]	
Bone scan					X		X		X	X[1]	

Patients enrolled as per prior versions of the protocol will follow the same schedule of activities and treatment/study discontinuation criteria.
**Includes Day 1, defined as the day subject receives his first dose of talazoparib.*

1. Unscheduled visits/assessments can be done anytime necessary to assess or follow up adverse events, at the patient's request, or per investigator decision, or to account for any insufficient, inadequate, or missed sample or assessments. Perform imaging if disease progression is suspected. Data are to be entered in the appropriate CRF. If medically required, additional ECGs will be done with results entered in the CRF; clinically significant findings will be captured as adverse events.
2. Approximately 28 days after permanent treatment discontinuation of study drug or before initiation of a new antineoplastic or investigational therapy whichever occurs first. Phone patients for adverse event follow-up if they do not come to the clinic.
3. Visits repeat every 12 weeks while on study drug. Hematology and serum chemistry assessments will be completed every 8 weeks by the central laboratory while on study drug.
4. Drug supply must be taken into account when scheduling visits during windows. Visit procedures may be split across the window to allow for drug resupply and completion of study procedures.
5. Measure blood pressure, heart rate, and temperature.
6. Assess 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. Measure weight.

7. Have the patient complete the questionnaires and collect blood samples before the first dose of study drug on day 1. These assessments will be performed:
   - At baseline (Day 1);
   - Every 2 weeks (prior to Study Week 9) weeks 9, 13, 17, 21 through Week 25, or radiographic progression, whichever is earlier;
   - Every 12 weeks after Week 25 until radiographic progression when no such progression had been previously documented;
   - During unscheduled visit(s) when no radiographic progression had been previously documented;
   - During safety follow up;
   - And at end of trial when study results are determined.
8. Collect serious and nonserious adverse event information from the time of signed informed consent for main screening through 28 days after the last dose of study drug (see Section 8 for details). Report any diagnosis of MDS or AML as an SAE any time after the first dose of talazoparib (Section 8.1.4.1 and Section 8.2.3). AEs and SAEs will be followed until the event or its sequelae resolves or stabilizes at a level acceptable to the investigator and the sponsor concurs with that assessment.
9. Instruct patient to self-administer talazoparib. The first dose is taken in the clinic; record the exact time of dose.
10. Refer to the central laboratory instruction manual for sample processing and for estimated turnaround time for laboratory results.
11. Central laboratory assessments (safety) are to be done at every scheduled visit, as well as unplanned, at the investigator's discretion, or to monitor adverse events or decide dosing modifications, noting that local safety assessments may also be performed but should not replace central lab assessments. Every effort should be taken to collect samples for central laboratory safety assessments even if unplanned. If serum chemistry and hematology laboratory tests were also done locally due to logistical issues, results from local laboratory assessments are to be entered in the appropriate CRF.
12. Collect blood samples for talazoparib PK at predose and 2 hours postdose in Week 1 (Day 1) and in Week 5, and predose in Weeks 9 and 13. Additional PK samples could be taken based on discretion of investigators, eg, adverse events. The actual time of the sample collection and the most recent dosing time before and after each collection will be recorded on the CRF.
13. Blood sample for CTC enumeration. Collect a minimum of 10 mL of whole blood at indicated visits. CTC samples must be shipped on day of collection and at room temperature. See Section 7.5 and Central Laboratory Manual.

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18. Radiographic imaging should be performed until radiographic progression is determined by independent central review. Soft tissue lesions will be followed only by RECIST 1.1 and bone lesions will be followed only by PCWG3 (modified RECIST1.1/PCWG3). Of note, soft tissue component of lytic or mixed bone lesions will be followed by RECIST 1.1; all other bone lesions will be followed by PCWG3. Tumor lesion assessments and overall assessment by RECIST 1.1 performed by the site will be entered in the CRF. Bone lesion assessments performed by the site will be entered in the CRF using the separate PCWG3 CRF pages.
19. Assessed via BPI-SF question 3 and recorded for each of the 7 consecutive days prior to each clinic visit after the Day 1 visit.
20. Use of any and all analgesics for prostate cancer pain is to be recorded for the 7 consecutive days prior to each clinic visit after the Day 1 visit.
21. Collect samples for analysis of PSA until determination of radiographic progression. Upon PSA progression or response, confirmation by a second consecutive value, at least 21 days later, is required.
22. Any time prior to dosing, document in the patient chart if patient is biologically capable of fathering a child or of exposing a fetus or partner via ejaculate. If capable, instruct the patient to use a condom to avoid pregnancy and/or fetal/partner exposure and instruct the patient to not donate sperm, for up to 4 months after talazoparib discontinuation. Only for these patients, investigators need to verify at every visit that the patient is following instructions provided as per Section 4.3. Investigators must document the conversation with the patient and, as applicable, confirm condom and contraception use or note changes in patient chart as per the schedule of activities.

BPI-SF, Brief Pain Inventory Short Form; CT, computed tomography; CTC, circulating tumor cells; CCI ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, European Quality of Life 5-Domain 5-Level Scale; exam, examination; FU, follow-up; ID, identification; lab, laboratory; MRI, magnetic resonance imaging; na, not applicable; PK, pharmacokinetics; unsched, unscheduled.

Table 4. Study Schedule of Activities: Long Term Follow-Up

Study Period or Visit	Long-Term Follow-Up	Long-term follow-up begins after safety follow-up; visits repeat every 8*- 12 weeks from the date of last dose until the patient dies, withdraws consent for follow-up, or the study is terminated.
Study Week	**Every 8- 12***	
Window (Days)	**±7**	
General Activities		
New antineoplastic therapy	X	Record all subsequent treatment information for patients starting any new antineoplastic therapies (approved or investigational).
Diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)	X	Record date of diagnosis of MDS or AML. Any diagnosis of MDS or AML will be reported as an SAE (Section 8.2.3). Provide tissue samples and any other supporting data used to enable the diagnosis of MDS or AML for central review if requested.
Survival status	X	Obtain survival status by any means including telephone, during a patient's clinic visit, chart review, or by communicating with an individual (eg, family, friend, referring health care provider) who is knowledgeable of the patient's survival status. If allowed by local laws and regulations, survival status may be obtained from public records for patients withdrawing consent from the study or for patients lost to follow-up.
Radiographic imaging	X	Only for patients who permanently discontinue study drug for any reason other than radiographic progression determined by independent central review when the patient has not withdrawn consent for follow-up.

**Every 8 weeks through week 25, then every 12 weeks thereafter.*

1. INTRODUCTION

1.1. Overview and Mechanism of Action

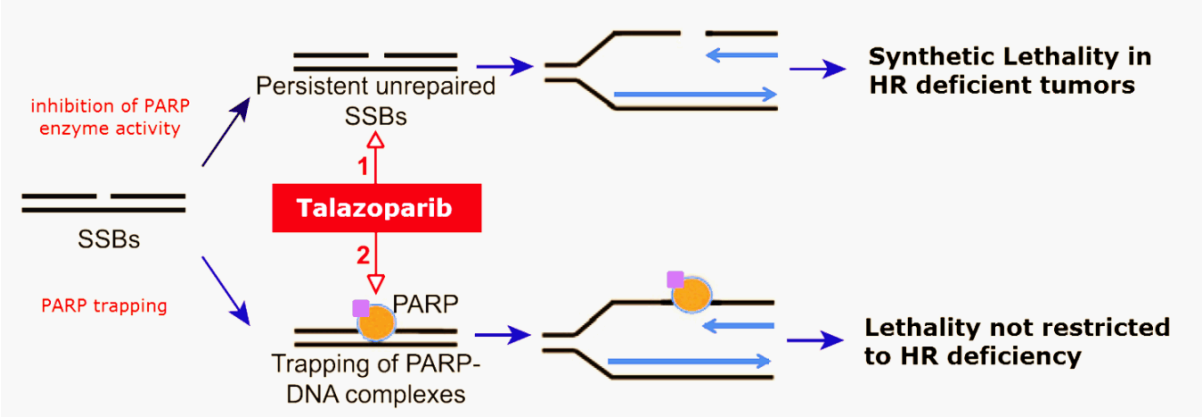
1.1.1. Overview

Talazoparib (also known as PF-06944076, MDV3800) is being investigated for the treatment of metastatic castration-resistant prostate cancer (mCRPC) with DNA damage repair deficiencies in men whose disease has previously progressed on novel hormonal therapy (NHT: enzalutamide and/or abiraterone acetate) given for the treatment of mCRPC and who were previously treated with taxane-based chemotherapy for metastatic disease.

1.1.2. Mechanism of Action/Indication

Talazoparib is a potent, orally bioavailable, small molecule poly (adenosine diphosphate [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: (1) inhibition of PARP1 and PARP2 catalytic activity, and (2) PARP trapping, a process in which PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, thereby preventing DNA repair, replication, and transcription (Murai et al, 2012).

Figure 1. Dual Cytotoxic Mechanisms of PARP Inhibitors



Source: Adapted from Reference 1

PARP = poly (adenosine diphosphate-ribose) polymerase.

Inhibition of PARP catalytic activity (upper pathway) interferes with the repair of single-strand breaks, leading to replication fork damage that requires homologous recombination DNA repair for cell survival. Trapping of PARP–DNA complexes with PARP inhibitor (lower pathway; PARP inhibitor represented by ■) also leads to replication fork damage with more DNA repair processes required for cell survival.

Single-agent treatment with talazoparib has demonstrated potent antitumor effects in tissue culture studies, mouse tumor xenograft models, and in Phase 1 studies in patients with solid tumors. Talazoparib has also been shown to enhance the cytotoxic effects of DNA-damaging chemotherapy, including temozolomide and irinotecan, in both in vitro and in vivo preclinical models.

1.2. Background and Rationale

1.2.1. Prostate Cancer

Prostate cancer is the second leading cause of cancer death in men. The American Cancer Society estimates that up to 180,890 men in the United States (US) will be diagnosed with prostate cancer and approximately 26,120 will die of the disease in 2016 (American Cancer Society, 2016). In Europe in 2012, prostate cancer was the third most common cancer site, with an estimated 416,700 new cases and 92,200 deaths (Ferlay et al, 2013).

The androgen receptor signaling axis, the principal driver of prostate cancer growth, has long been targeted by castration. However, a proportion of tumors progress despite castrate levels of testosterone, at which point the disease is considered castration-resistant. Castration-resistant prostate cancer (CRPC) represents a lethal transition in the progression of prostate cancer, with most patients ultimately succumbing to the disease. Molecular profiling studies have revealed that the androgen receptor remains functional in a majority of progressing tumors. Rationally designed therapies targeting the androgen receptor signaling pathway (Donovan et al, 2010) include enzalutamide, a novel androgen receptor antagonist that is active in the presence of androgen receptor overexpression (Tran et al, 2009), and abiraterone acetate/prednisone (de Bono et al, 2011), an inhibitor of 17,20-lyase (an androgen biosynthetic enzyme overexpressed in CRPC) (Stanbrough et al, 2006; Holzbeierlein et al, 2004). Prior to the recent approval of novel hormonal therapies (NHT) (enzalutamide, abiraterone acetate/prednisone), the only approved therapies for metastatic CRPC were docetaxel, cabazitaxel and sipeleucel-T. The approval of NHTs in metastatic CRPC previously treated with docetaxel (De Bono et al, 2011; Scher et al, 2012) represented a therapeutic advance for these patients.

Clinical experience with these therapies validated findings that the androgen receptor remains active despite androgen deprivation in men with CRPC, but resistance to these second-generation agents invariably occurs. Median survival remains low (approximately 15-18 months) for men with metastatic CRPC who had previously received docetaxel in studies of enzalutamide and abiraterone acetate/prednisone (Scher et al, 2012; de Bono et al, 2011). Furthermore, in the COMET-1 study of men with metastatic CRPC who had previously received both docetaxel and novel hormonal therapy, the median survival for those who received cabozantinib or prednisone was even lower at 11.0 months and 9.8 months, respectively (Smith et al, 2015). No approved therapy has been tested in the target population of this study, as all currently approved treatments for symptomatic metastatic CRPC (including soft tissue disease) after docetaxel-based chemotherapy were tested in patients who had not received novel hormonal therapy. Thus, the target population in this study has an unmet medical need deserving of potentially promising experimental therapies.

The key efficacy results of phase 2 and 3 studies in metastatic CRPC after chemotherapy (primarily docetaxel) are presented in Table 5.

Table 5. Key Efficacy Results of Phase 2 and 3 Studies in Metastatic CRPC After Chemotherapy (Primarily Docetaxel)

Study	Prior Novel Hormonal Therapy	Treatment vs Comparator	ORR	Radiographic PFS (HR; median)	Overall Survival (HR; median)
SPARC	No	Satraplatin vs placebo (background prednisone)	8% vs 0.7%	HR = 0.67 11 vs 10 wk	HR = 0.98 61 vs 61 wk
CRPC2; AFFIRM	No	Enzalutamide vs placebo	29% vs 4%	HR = 0.40 8.3 vs 2.9 mo	HR = 0.63 18.4 vs 13.6 mo
COU-AA-301	No	Abiraterone vs placebo (background prednisone)	14% vs 3%	HR = 0.67 5.6 vs 3.6 mo	HR = 0.65 14.8 vs 10.9 mo
EFC6193; TROPIC	No	Cabazitaxel vs mitoxantrone (background prednisone)	14% vs 4%	HR = 0.74 2.8 vs 1.4 mo	HR = 0.70 15.1 vs 12.7 mo
COMET-1	Yes	Cabozantinib vs prednisone	Not reported	HR = 0.50 5.5 vs 2.8 mo	HR = 0.90 11.0 vs 9.8 mo (NS)
TOPARP-A	Yes	Olaparib (no comparator)	71% (5 of 7) in BM+ subgroup[1,2]	HR = 0.24 9.8 vs 2.7 mo (BM+ vs -)	HR = 0.47 13.8 vs 7.5 mo (BM+ vs -)

Abbreviations:
SPARC: Satraplatin and Prednisone Against Refractory Prostate Cancer; TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer; COMET-1: Carvedilol Or Metoprolol European Trial;
TOPARP-A: Trial of Olaparib in Patients With Advanced Castration Resistant Prostate Cancer, part A.

Source: Sternberg et al, 2009; Scher et al, 2012; de Bono et al, 2011; de Bono et al, 2010; Smith et al, 2015; Mateo et al, 2015, Novel hormonal therapy is defined as enzalutamide and/or abiraterone acetate/prednisone after chemotherapy.

1. All 7 patients with BRCA2 loss responded; 5 of 7 biomarker-positive patients with measurable disease had an objective response in soft tissue.
2. Response rates of 88% vs 6% for BM+ vs BM– were based on a composite endpoint and not solely on soft tissue responses as for all other studies.

BM+ vs -, biomarker positive versus negative; CRPC, castration-resistant prostate cancer; HR, hazard ratio; mo, months; NS, not significant; ORR, objective response rate; PFS, progression-free survival; vs, versus; wk, weeks.

1.2.2. PARP Inhibition

PARP1 and PARP2 play important roles in DNA repair (Schreiber et al, 2006; Curtin NJ. 2005). Following DNA damage, PARP1 and PARP2 bind to single-stranded DNA breaks, cleave nicotinamide adenine dinucleotide, and attach multiple ADP-ribose units to chromatin- associated proteins, including histones and PARP1 itself (Gibson & Kraus, 2012; Schreiber et al, 2002; Amé et al, 1999; Johansson 1999). The outcome is a highly negatively charged protein, which leads to the unwinding of the DNA strands and recruitment of proteins to repair the damaged DNA through the base-excision repair process. When PARP1 and PARP2 are inhibited, single-strand DNA breaks persist, resulting in stalled

replication forks and conversion of single-strand breaks into double-strand breaks. These breaks must be repaired by homologous recombination or nonhomologous end joining or they may become lethal. Thus, inhibition of PARP catalytic activity results in synthetic lethality as defects in homologous recombination DNA repair prevent double strand breaks from being repaired, thereby killing the cell, including cancer cells.

In addition, PARP inhibitors bind to PARP-DNA complexes trapping them, thereby inhibiting DNA repair, replication, and transcription, with associated cytotoxic effects on cancer cells. Although other PARP inhibitors possess both activities, in vitro studies demonstrated that talazoparib is a more potent PARP trapper than other PARP inhibitors in clinical development (Hopkins et al, 2015; Murai et al, 2014).

1.2.3. PARP Inhibitors as a Potential Targeted Therapeutic in Metastatic CRPC

Proof of concept that PARP inhibition may treat prostate cancer with DNA damage repair deficiency was established in a Phase 2 study (TOPARP-A) with the PARP inhibitor olaparib (Mateo et al, 2015). In the TOPARP-A study, 50 patients with metastatic CRPC were treated with the PARP inhibitor olaparib (400 mg orally twice daily). All had been previously treated with docetaxel, 98% with abiraterone or enzalutamide, and 58% with cabazitaxel. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) score of 0 to 2; disease progression per Prostate Cancer Working Group 2 (PCWG2) and/or Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1); 5 or more circulating tumor cells (CTC) per 7.5 mL of blood; and consented to a fresh tumor biopsy. No prior exposure to platinum, cyclophosphamide, mitoxantrone, or other PARP inhibitors was permitted. Forty-nine patients were evaluable for response based on a composite endpoint of objective response according to RECIST 1.1, a reduction of at least 50% in prostate-specific antigen (PSA), or a confirmed reduction in CTC counts from 5 or more cells per 7.5 mL of blood to less than 5 cells per 7.5 mL of blood in patients with an identified homozygous deletion and/or putative deleterious mutation in DNA repair genes. Sixteen of 49 evaluable patients (33%) had a response and the median duration of treatment was 40 weeks for responding patients. Treatment with olaparib led to a response based on the composite endpoint definition in 14 of 16 patients (88%) with identified genomic deficiencies associated with DNA damage repair. On the other hand, only 2 responses (6%) were seen in 33 patients without such genomic deficiencies.

Of the 32 evaluable patients (65% of the 49 evaluable patients) who had measurable disease at baseline per RECIST 1.1, 7 patients had DNA damage repair deficiencies and 5 of those 7 (71%) had a partial response (PR) per RECIST 1.1. Patients with DNA damage repair deficiencies had longer median radiographic progression-free survival (PFS) (9.8 vs 2.7 months) and median overall survival (13.8 vs 7.5 months) compared with patients without DNA damage repair deficiencies.

In an integrated analysis of somatic and germline mutation status in tumor biopsies from 150 patients with metastatic CRPC, 22.7% of cases had mutations in DNA repair genes associated with sensitivity to a PARP inhibitor, including BRCA2, BRCA1, CDK12, FANCA, RAD51B, RAD51C, MLH1, MSH2, and ATM. Loss of BRCA2 was observed in 12.7% of cases (approximately 90% of these were biallelic loss), and 8% harbored a germline

alteration. Another clinical targeted sequencing analysis of prostate cancer identified similar frequencies of somatic and germline alterations in DNA damage repair genes BRCA2, BRCA1, and ATM (Abida et al, 2015).

PARP1 and PARP2 play important roles in DNA repair (Schreiber et al, 2006; Curtin, 2005). Following DNA damage, PARP1 and PARP2 bind to single-stranded DNA breaks, cleave nicotinamide adenine dinucleotide (NAD+), and attach multiple ADP-ribose units to the target protein, including itself (Gibson & Kraus, 2012; Schreiber et al, 2002; Amé et al, 1999; Johansson, 1999). The outcome is a highly negatively charged protein, which leads to the unwinding of the DNA strands and recruitment of proteins to repair the damaged DNA through the base-excision repair process. When PARP1 and PARP2 are inhibited, single-strand DNA breaks persist, resulting in stalled replication forks and conversion of single-strand breaks into double-strand breaks. These breaks must be repaired by homologous recombination or nonhomologous end joining or they may become lethal.

Talazoparib (also known as PF-06944076, MDV3800, BMN 673) 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). 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). PARP inhibition exhibits an enhanced cytotoxic effect in cancers with DNA damage repair deficiencies. The majority of responses in the TOPARP-A study of the PARP1 and PARP2 inhibitor olaparib in metastatic CRPC (Mateo et al, 2015, described in Section 1.2) were observed in men with known DNA damage repair deficiencies. In this phase 2 study of olaparib monotherapy, 16 of 49 evaluable patients with metastatic CRPC (33%) had mutations and/or deletions in genes involved in homologous recombination or other DNA repair pathways. Of the 16 patients (33%) who responded to treatment with olaparib, 14 (88%) had mutations in DNA repair genes. These data suggest that PARP inhibition may be a useful strategy for the treatment of tumors in men with metastatic CRPC, especially those harboring DNA repair pathway deficiencies. In an integrated analysis of somatic and germline mutation status in tumor biopsies from 150 patients with metastatic CRPC, 22.7% of cases had mutations in DNA repair genes associated with sensitivity to a PARP inhibitor, including BRCA2, BRCA1, CDK12, FANCA, RAD51B, RAD51C, MLH1, and ATM (Robinson et al, 2015). Loss of BRCA2 was observed in 12.7% of cases (approximately 90% of these were biallelic loss), and 8% harbored a germline alteration in BRCA2, BRCA1, or ATM. Another clinical targeted sequencing analysis of prostate cancer identified similar frequencies of somatic and germline alterations in DNA damage repair genes BRCA2, BRCA1, and ATM (Abida et al, 2015).

1.2.4. Clinical Data Supporting PARP Inhibition as a Potential Targeted Therapeutic in Metastatic CRPC

In the TOPARP-A study (Mateo et al, 2015), 50 patients with metastatic CRPC were treated with the PARP inhibitor olaparib (400 mg orally twice daily). All had been previously treated with docetaxel, 98% with abiraterone or enzalutamide, and 58% with cabazitaxel. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) score of 0 to 2; disease progression per Prostate Cancer Working Group 2 (PCWG2) and/or Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1); 5 or more circulating tumor cells (CTC) per 7.5 mL of blood; and consented to a fresh tumor biopsy. No prior exposure to platinum, cyclophosphamide, mitoxantrone, or other PARP inhibitors was permitted. Forty-nine patients were evaluable for response based on a composite endpoint of objective response according to RECIST 1.1, a reduction of at least 50% in prostate-specific antigen (PSA), or a confirmed reduction in CTC counts from 5 or more cells per 7.5 mL of blood to less than 5 cells per 7.5 mL of blood in patients with an identified homozygous deletion and/or putative deleterious mutation in DNA repair genes. Sixteen of 49 evaluable patients (33%) had a response and the median duration of treatment was 40 weeks for responding patients. Treatment with olaparib led to a response based on the composite endpoint definition in 14 of 16 patients (88%) with identified genomic deficiencies associated with DNA damage repair. Of the 32 evaluable patients (65% of 49) who had measurable disease at baseline per RECIST 1.1, 7 patients had DNA damage repair deficiencies and 5 of those 7 (71%) had a partial response (PR) per RECIST 1.1. Tumor regression in bone was documented on whole-body magnetic resonance imaging (MRI) in a patient with an ATM defect. Patients with DNA damage repair deficiencies had longer median radiographic progression-free survival (PFS) (9.8 vs 2.7 months) and median overall survival (13.8 vs 7.5 months) compared with patients without DNA damage repair deficiencies. The median duration of olaparib treatment for all patients was 12 weeks. Grade 3 and 4 adverse events included anemia (20% of patients), fatigue (12%), leukopenia (6%), thrombocytopenia (4%), and neutropenia (4%). At least 1 dose reduction was required in 13 patients (26%), primarily due to anemia; 3 patients (6%) discontinued due to adverse events.

1.3. Summary of Relevant Clinical Experience With Talazoparib

As of 31 Jan 2018, talazoparib has been evaluated in approximately 659 patients and 18 healthy volunteers in both company-sponsored and investigator-sponsored studies in hematologic malignancies and solid tumors at doses up to 2 mg/day. Results from company-sponsored studies are summarized in the following sections.

1.3.1. Efficacy

A phase 1 clinical study supports the efficacy of talazoparib monotherapy at 1 mg once daily.

PRP-001 is a phase 1, open-label, safety, pharmacokinetics (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 01 Sep 2016, data cutoff date for the primary analysis, objective responses (complete response [CR] or PR) per RECIST 1.1 were observed in 7 of 14 patients (50%) with breast cancer and 5 of 12 patients (41.7%) with ovarian/primary peritoneal cancer

with deleterious germline BRCA mutations treated at 1 mg/day; clinical benefit (CR, PR, or stable disease ≥24 weeks) was observed in 12 of 14 patients (85.7%) and 8 of 12 patients (66.7%), respectively.

Study 673-201 (ABRAZO) is a Phase 2, 2-stage, 2-cohort study of talazoparib in patients with germline BRCA mutation and locally advanced and/or metastatic breast cancer. As of December 2016, the confirmed objective response rate (CRs and PRs) was 20.8% for cohort 1 (95% confidence interval [CI]: 10.47, 34.99), including 2 CRs (4.2%), and 37.1% for cohort 2 (95% CI: 21.47, 55.08) per independent central radiology assessment. The objective response rate across both cohorts was 27.7% (95% CI: 18.45, 38.62), demonstrating clinically meaningful responses in this population with a poor prognosis and a high unmet medical need.

Activity of talazoparib in women with germline BRCA 1/2 mutation and locally advanced breast cancer has been confirmed in a phase 3 study (EMBRACA, Litton et al, 2018) comparing the safety and efficacy of 1 mg/day talazoparib versus physician's-choice of chemotherapy (PCT) which included capecitabine, eribulin, gemcitabine, or vinorelbine. The median progression-free survival was 8.6 months for patients treated with talazoparib, vs 5.6 months for patients treated with physician's-choice chemotherapy (HR = 0.542, *P* <.0001).

Additional and updated information on the clinical efficacy of talazoparib is provided in the talazoparib investigator's brochure.

1.3.2. Safety

Aggregate safety data from 5 open-label studies, including 1 randomized, company-sponsored clinical study (PRP-001, 673-201, 673-301, MDV3800-13, and MDV3880-15: N = 502 patients) evaluating talazoparib monotherapy in solid tumors at the proposed dose of 1 mg/day provide the basis for the reported treatment-emergent adverse events (TEAEs). All causality TEAEs reported in ≥20% of patients administered single-agent talazoparib 1 mg/day are related to myelosuppression (anemia, neutropenia), GI toxicity (nausea, diarrhea, vomiting, constipation, and decreased appetite), fatigue, headache, and alopecia.

Grade 3 or 4 TEAEs in ≥5% of patients were associated with myelosuppression.

Study drug-related TEAEs occurring in ≥20% of patients in the talazoparib 1 mg/day population were anemia (45.8%), fatigue (36.1%), nausea (32.5%), neutropenia (21.9%), and alopecia (20.1%). Grade 3 or 4 drug-related TEAEs occurring in ≥5% of patients were anemia (34.1%), neutropenia (13.9%), thrombocytopenia (10.6%), and platelet count decreased (5.4%).

A total of 23 of 502 (4.6 %) patients in the talazoparib 1 mg/day population had a TEAE that led to death, 8 deaths were associated with the malignancy under study (including 1 subject whose death was also associated with pneumonia); 2 deaths were associated with dyspnea; 2 with general physical health deterioration; 3 with disease progression; and 1 each with lung infection, cerebral hemorrhage, cerebrovascular accident, fatigue (event term later changed to

failure to thrive), liver disorder, neurological symptom, respiratory failure, and veno-occlusive liver disease. Of these, only veno-occlusive liver disease was assessed as related to study drug by the investigator.

Serious adverse events (SAEs) occurred in 164 of 502 patients (32.7%) in the talazoparib 1 mg/day population. SAEs occurring in ≥2% of patients were anemia (5.2%) and dyspnea (2.2%) and pleural effusion (2.2%). Forty-seven patients had SAEs considered related to study drug. Study drug-related SAEs occurring in ≥1% of patents were anemia (4.6%), thrombocytopenia (1.2%) and platelet count decreased (1.2%).

Twenty (20) of 502 patients (4.0%) in the talazoparib 1 mg/day population discontinued study drug due to a TEAE. The events that led to study drug discontinuation were anemia (3 patients), increased alanine aminotransferase (ALT, 2 patients), and accidental overdose, increased aspartate aminotransferase (AST), bradycardia, metastatic breast cancer, cerebral hemorrhage, dyspnea, glioblastoma multiforme, headache, metastases to meninges, muscular weakness, neutropenia, obstructive airways disorder, thrombocytopenia, transient ischemic attack, and vomiting (1 patient each).

Among the 502 patients in the Talazoparib 1 mg/day population, 63.9% had a TEAE that led to dose reduction and 61.2% had a TEAE that led to dosing interruption. The most common TEAEs that led to dose reduction or interruption were associated with myelosuppression.

In the EMBRACA trial, the adverse events observed with talazoparib were consistent with findings from previous trials. The most common adverse events (AEs) observed with talazoparib (any grade in at least 15% of patients) were anemia (52.8%), fatigue (50.3%), nausea (48.6%), neutropenia (34.6%), headache (32.5%), thrombocytopenia (26.9%), alopecia (25.2%), vomiting (24.8%), diarrhea (22%), constipation (22%), decreased appetite (21.3%), back pain (21%) and dyspnea (17.5%). The incidence of SAEs was 31.8% in the talazoparib arm and 29.4% in the PCT chemotherapy arm. Discontinuations due to AEs occurred in 7.7% of patients in the talazoparib arm and 9.5% of patients in the PCT chemotherapy arm.

For additional important safety information from other talazoparib studies, please consult the current talazoparib investigator's brochure.

1.3.3. Pharmacokinetics

Talazoparib plasma exposure was dose proportional in the dose range of 0.025 mg to 2 mg once a day suggesting linear PK. Talazoparib absolute bioavailability is at least 54.6%. After administration of a single 1 mg dose of talazoparib to cancer patients, the median T_{max} ranged from 0.5 to 2.0 hours across studies. Administration of a single 0.5 mg dose of talazoparib to healthy subjects with food (a high-fat, high-calorie meal) had no impact on the area under the plasma concentration time curve (AUC) while reduced the C_{max} by 46%. The reduction in the rate of absorption with food is not expected to be clinically relevant as efficacy is driven by total overall exposure for the typical targeted anti-cancer therapies. Therefore, talazoparib can be taken without regard of food.

Mean talazoparib binding to human plasma proteins is 74%. Population PK analysis showed that talazoparib apparent steady-state volume of distribution (Vss/F) was 420 L, which is significantly greater than total body water (42 L), indicating that talazoparib distributes to peripheral tissues.

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

Talazoparib was eliminated slowly with a mean terminal plasma half-life (t½) of 89.8 hours. Talazoparib accumulated after 1 mg once a day dosing with a median accumulation ratio ranging from 2.33 to 5.15, consistent with its t½. Population PK analysis showed that talazoparib CL/F was 6.45 L/hr. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose. Population PK analysis showed that talazoparib CL/F was reduced by 14.4% and 37.1% in patients with mild renal impairment (creatinine clearance [CrCl], 60 to 89 mL/min) and moderate renal impairment (30 mL/min ≥ CrCl <60 mL/min), respectively, compared to that of patients with normal renal function (CrCl ≥90 mL/min). No dose adjustment is recommended for patients with mild renal impairment. For patients with moderate renal impairment, the recommended dose of talazoparib is 0.75 mg once a day.

In vitro studies showed that talazoparib is a substrate for the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Population PK analysis indicated that concomitant administration of strong P gp inhibitors with talazoparib increased talazoparib exposure by 44.7% relative to talazoparib administered alone. Guidelines for concomitant use of talazoparib with P-gp inhibitors or inducers and BCRP inhibitors are provided in Section 5.10.

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

1.4. Summary of Relevant Nonclinical Experience With Talazoparib

1.4.1. Nonclinical Pharmacology of Talazoparib

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 with inhibitory constant (Ki) values of 1.2 nM and 0.87 nM, respectively (Wang et al, 2016). Talazoparib was approximately 3.4- to 8.3-fold more potent than other PARP inhibitors in clinical development (veliparib, rucaparib, olaparib) in inhibiting PARP1 catalytic activity (Shen et al, 2013). In addition, talazoparib was approximately 40-fold more potent than olaparib in stimulating the formation of stable PARP1-DNA complexes (Murai et al, 2014).

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

1.4.2. 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 [^{14}C]-talazoparib has high metabolic stability (>90%) over 2 hours. A minimal extent or a lack of metabolism for [^{14}C]-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. Talazoparib is not a substrate of metabolizing CYP450 enzymes. 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.

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

1.4.3. 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 (ECG) evaluations after a repeat-dose oral administration in dogs (repeat-dose toxicity studies). Talazoparib had no effect on ophthalmologic endpoints 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's brochure.

1.5. Talazoparib Benefits and Risks Assessment

The doses of talazoparib in this protocol are supported by nonclinical studies and phase 1-3 studies in patients with advanced malignancies. Adverse drug reactions with talazoparib include myelosuppression, gastrointestinal toxicity, fatigue, and alopecia. Hepatotoxicity, second primary nonhematologic malignancies and pneumonitis are adverse events of special interest per the investigator's brochure. Seven AEs of second primary nonhematologic malignancies were reported in 6 patients (squamous cell carcinoma of skin [2 patients], and basal cell carcinoma, glioblastoma multiforme, intraductal proliferative breast lesion, neoplasm skin, and ovarian neoplasm [1 patient each, respectively]). These second primary malignancies were mostly skin malignancies. In general, latency to diagnosis of the malignancy was relatively short, making a relationship with talazoparib unlikely. Diagnoses of myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) have been reported in patients who received poly(adenosine diphosphate [ADP] ribose) polymerase (PARP) inhibitors. Overall, MDS/AML has been reported in 2 (1 MDS and 1 AML case) out of 561 solid tumor patients treated with talazoparib in clinical studies.

The activity of talazoparib as monotherapy and in combination with other agents is being evaluated in multiple indications. Recent results from the EMBRACA study (Litton et al, 2018) a phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy (PCT) in patients with advanced breast cancer and a germline *BRCA* mutation, demonstrated that single-agent talazoparib at 1 mg/day significantly prolonged progression-free survival in HER2-negative advanced breast cancer patients with a germline BRCA 1/2 mutation compared to PCT. Data from the study indicate that talazoparib was generally well tolerated with minimal non-hematologic toxicity and few AEs associated with treatment discontinuations.

The benefit-risk profile of talazoparib in prostate cancer patients is not yet characterized.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure.

1.6. Rationale for Talazoparib Dose

Talazoparib has demonstrated efficacy at a dose of 1 mg/day. Talazoparib 1 mg/day orally will be administered until radiographic progression is determined by independent central review, unacceptable toxicity, withdrawal of consent, or death. In addition, talazoparib can continue to be administered upon disease progression only if, in the opinion of the investigator the patient is clinically benefitting, no new concurrent systemic therapy is started, and the sponsor is notified. For patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30-59 mL/min/1.73 m^2 as per central laboratory) at screening, the starting dose will be 0.75 mg/day. Study drug should not be discontinued based solely on PSA or CTC count increases.

2. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and corresponding endpoints are provided in Table 6, below.

Table 6. Objectives and Endpoints for Study

Primary Objective(s):	**Primary Endpoint(s):**
To evaluate the efficacy, of single agent talazoparib in DDR+ mCRPC as measured by best objective response rate (ORR).	Best ORR: The proportion of patients with a best overall soft tissue response of CR or PR per RECIST 1.1 by independent central review. Soft tissue responses must be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated CT or MRI with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria by independent central review.
Secondary Objective(s):	**Secondary Endpoint(s):**
To evaluate efficacy with respect to the following parameters: • Time to objective response; • Duration of response; • Proportion of patients with prostate-specific antigen (PSA) decrease ≥50%; • Proportion of patients with conversion of circulating tumor cell (CTC) count; • Time to PSA progression; • Radiographic progression-free survival (PFS); • Overall survival.	Time to objective response: The time from first dose of talazoparib to the first objective evidence of soft tissue response with no evidence of confirmed bone disease progression on bone scan per PCWG3. Soft tissue response is defined as a best overall response of CR or PR per RECIST 1.1 by independent central review. The response must be confirmed at least 4 weeks later with a repeated CT/MRI. Duration of response: The time from the first objective evidence of soft tissue response (subsequently confirmed) per RECIST 1.1 by independent central review and no evidence of confirmed bone disease progression per PCWG3 to the first subsequent objective evidence of radiographic progression or death due to any cause, whichever occurs first. Radiographic progression is defined as soft tissue progression per RECIST 1.1 by independent central review or bone disease progression per PCWG3 by independent central review. Proportion of patients with PSA response ≥50%: The proportion of patients with confirmed PSA decline ≥50% compared to baseline. For CTC counts: • The proportion of patients with conversion of CTC count: The proportion of patients with a CTC count ≥5 CTC per 7.5 mL of blood at study entry that decreases to <5 CTC per 7.5 mL of blood any time on study. • The proportion of patients with a CTC count of 1 or more per 7.5 mL of blood at study entry that decreased to CTC=0 per 7.5 mL of blood any time on study. • The proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline. Time to PSA progression: The time from first dose of talazoparib to the date that a ≥25% increase in PSA with an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline) is documented, confirmed by a second consecutive PSA value obtained ≥3 weeks (21 days) later. Radiographic PFS: The time from first dose of talazoparib to radiographic progression in soft tissue per RECIST 1.1 by independent central review, in bone per PCWG3 by independent central review, or death, due to any cause whichever occurs first. Overall survival: Defined as the time from first dose of talazoparib to death due to any cause.

Table 6. Objectives and Endpoints for Study

To evaluate the safety of talazoparib in this patient population. To evaluate the following patient-reported outcomes: • Time to deterioration in patient reported pain as assessed by the Brief Pain Inventory Short Form (BPI-SF); • Change from baseline in patient reported pain per BPI-SF; • Change from baseline in patient-reported outcome general health status as assessed by the European Quality of Life 5-Domain 5-Level Scale (EQ-5D-5L). To evaluate the pharmacokinetics (PK) of talazoparib.	Assessment of safety will include adverse events, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, vital signs, and clinical laboratory tests. Evaluate the following patient-reported outcomes: • Time to deterioration in patient reported pain as assessed by the Brief Pain Inventory Short Form (BPI-SF); • Change from baseline in patient reported pain per BPI-SF; • Change from baseline in patient-reported outcome general health status as assessed by the European Quality of Life 5-Domain 5-Level Scale (EQ-5D-5L). Assessment of the pharmacokinetics of talazoparib will include pre-dose trough and post-dose plasma concentrations for talazoparib.
CCI [redacted]	[redacted]

3. STUDY DESIGN

3.1. Overall Study Design and Plan: Description

This is an international, phase 2, open-label, soft tissue response rate study of talazoparib, a PARP inhibitor in development for the treatment of cancer. PARP inhibition has been shown to produce clinical responses in metastatic CRPC, particularly in patients with DNA damage repair deficiencies. PARP inhibitors are thought to induce cell toxicity by inhibiting PARP catalytic activity as well as by trapping PARP-DNA complexes, which prevent DNA repair, replication, and transcription. Nonclinical studies have shown that talazoparib has potent cytotoxic effects via both mechanisms, with greater cell toxicity from PARP trapping.

In this study, patients will be evaluated at prescreening (optional) or screening for DNA damage repair deficiencies as assessed by a gene mutation biomarker panel. At least 100 men with measurable soft tissue disease (per RECIST1.1) and progressive metastatic CRPC and DNA damage repair deficiencies likely to sensitize to PARP inhibition will be enrolled. Eligible patients must have previously received 1 to 2 chemotherapy regimens including at least 1 taxane-based regimen for treatment of metastatic prostate cancer, and progressed on at least 1 line of novel hormonal therapy (enzalutamide and/or abiraterone acetate/prednisone) for treatment of metastatic CRPC.

Patients must consent to submit sufficient tumor tissue (de novo tumor biopsy or archival tissue) for targeted next-generation sequencing to determine DNA damage repair gene deficiencies for eligibility. Previous identification of DNA repair deficiencies likely to sensitize to PARP inhibition, using the FoundationOne CDx™ test may be considered for eligibility (with sponsor approval). Biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel may not be performed for the sole purpose of determining study eligibility.

The primary efficacy endpoint is best ORR by modified RECIST1.1/PCWG3. An objective response is defined as a best overall response of CR or PR per RECIST 1.1. Responses must be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated computed tomography (CT)/MRI and with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria by independent central review.

Talazoparib 1 mg/day orally will be administered until radiographic progression is determined by independent central review, unacceptable toxicity, withdrawal of consent, or death. In addition, talazoparib can continue to be administered upon disease progression only if, in the opinion of the investigator the patient is clinically benefitting, no new concurrent systemic therapy is started, and the sponsor is notified. For patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30-59 mL/min/1.73 m^2 per central laboratory) at screening, the starting dose will be 0.75 mg/day. Study drug should not be discontinued based solely on PSA or CTC count increases.

Study periods include prescreening (optional), screening, treatment, safety follow-up, and long-term follow-up. Safety follow-up after permanent discontinuation of study drug treatment will occur approximately 28 days after the last dose of study drug or before initiation of a new antineoplastic or investigational therapy, whichever occurs first.

Long-term follow-up will occur every 8 (if study treatment discontinuation is prior to week 25) to 12 weeks (if study treatment discontinuation is at or beyond week 25) after safety follow-up. Radiographic imaging should continue during long-term follow-up for patients who discontinue study drug for any reason other than radiographic progression determined per protocol, withdrawal of consent for follow-up, or death. Survival status, new antineoplastic therapy(ies), and diagnosis of myelodysplastic syndrome and acute myeloid leukemia will be assessed until the study is terminated.

CCI [redacted]

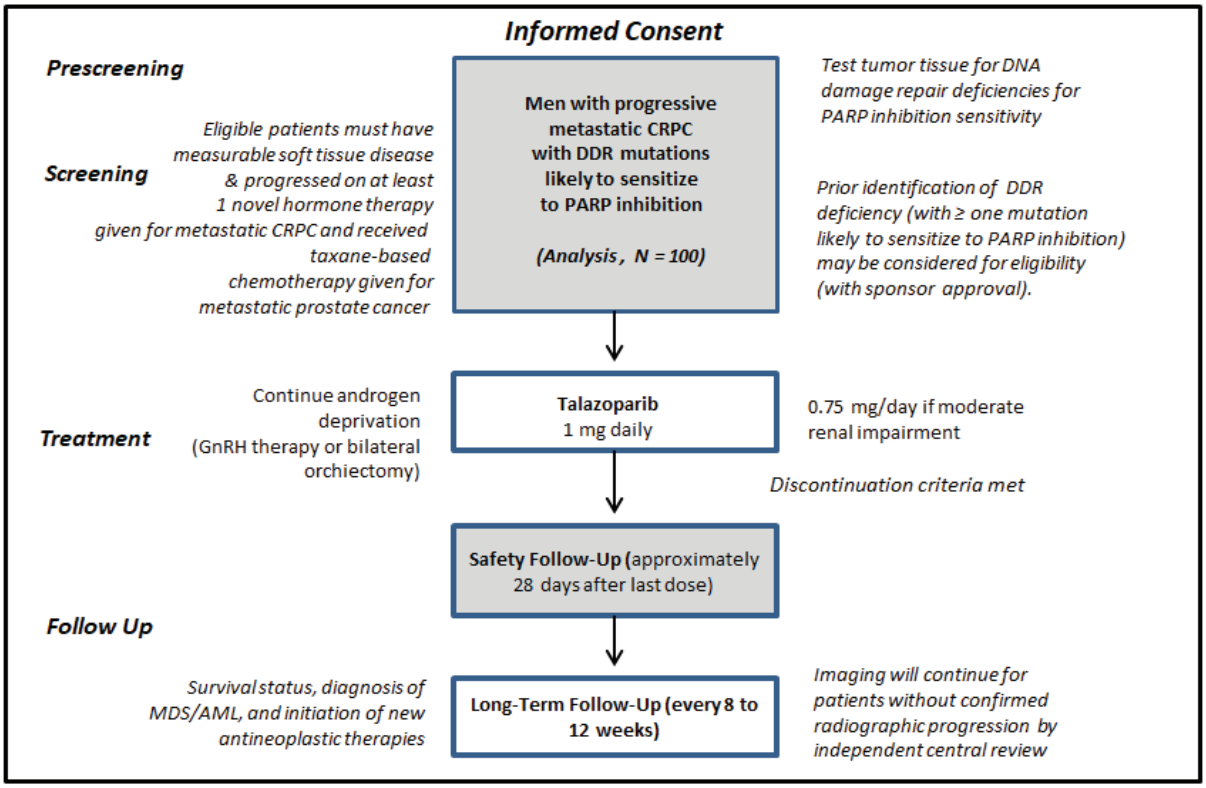
Patient-reported outcomes will be assessed to determine time to deterioration in pain using the Brief Pain Inventory Short Form (BPI-SF) and general health status using the EQ-5D-5L health questionnaire. These assessments will be performed:

- At baseline (Day 1);
- Every 2 weeks (prior to Study Week 9) , weeks 9, 13, 17, 21 through Week 25, or radiographic progression, whichever is earlier;
- Every 12 weeks after Week 25 until radiographic progression when no such progression had been previously documented;
- During unscheduled visit(s) when no radiographic progression had been previously documented;
- During safety follow up;
- And at end of trial when study results are determined.

3.2. Study Schematic

The study schematic is provided in Figure 2 (below).

Figure 2. Study Schematic



Key assessments: Bone scan, CT/MRI, PSA, PK, CCI CTC, patient-reported outcomes
Optional: Prescreening for tumor tissue analysis for eligibility purposes

3.3. Blinding

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

The primary endpoint analysis will be performed when the last enrolled patient who does not discontinue treatment prematurely, completes at least 6 months of study drug treatment, withdraws consent, discontinues from the study, or dies, whichever occurs first.

3.5. Discussion of Study Design and Rationale for Dose Selection

Treatment of men with metastatic CRPC previously treated with taxane-based chemotherapy and who progressed on novel hormonal therapy is an area of high unmet need. No therapy is approved for this patient population, and National Comprehensive Cancer Network (NCCN) guidelines do not specifically address treatment in this late disease stage. Study C3441006 (MDV3800-06) is based on nonclinical studies supporting the sensitivity of prostate tumors with DNA damage repair deficiencies, which may sensitize to PARP inhibition, and clinical evidence demonstrating a high response rate to the PARP inhibitor, olaparib, in a genomically selected subset of men with metastatic CRPC (the TOPARP-A study, discussed

in Section 1.2). Talazoparib has cytotoxic effects believed to be caused by inhibition of the catalytic activity of PARP-dependent DNA repair and suppression of DNA synthesis and transcription at sites of PARP trapping.

This study will evaluate patients at prescreening (optional) or screening for DNA damage repair deficiencies as assessed using a biomarker panel of gene mutations. The patients will be evaluated for gene mutations in a panel of genes that, when mutated, are likely to sensitize to PARP inhibition.

The sample size requirement for patients with measurable soft tissue disease supports the primary endpoint of best ORR, which is a clinically relevant endpoint with precedent in oncology indications where high unmet need exists. Cabazitaxel is a possible therapy indicated for these patients and its previous use is permitted. Similarly, radium-233 is a possible therapy for patients with symptomatic bone metastatic CRPC without visceral metastases and its previous use is permitted.

Mechanisms of resistance to PARP inhibition may be shared with DNA-damaging agents such as cyclophosphamide and or mitoxantrone; thus, these agents and prior treatment with a PARP inhibitor in an experimental setting are excluded to maximize the likelihood of treatment efficacy. Similarly, treatment with platinum-based therapies in the 6 months prior to screening, or progression on prior platinum-based therapy at any time in the past, will exclude participation. Treatment with chemotherapy (eg, docetaxel, cabazitaxel) within 28 days of Day 1 and on study is also prohibited given the heightened risk of myelosuppression. A known diagnosis of myelodysplastic syndrome or acute myeloid leukemia and central laboratory hematology values below specified thresholds for hemoglobin, absolute neutrophil count, and platelet count at screening are also exclusionary given the predicted risk of dose-dependent myelosuppression. Pulmonary function testing is not mandated given the rarity of pneumonitis reports with exposure to other PARP inhibitors. Current or anticipated use within 7 days prior to first dose of study drug or anticipated use during the study of strong P-gp inhibitors is exclusionary. For a list of strong P-gp inhibitors, refer to Section 5.11.

C3441006 (MDV3800-06) will include an efficacy assessment schedule of every 8 weeks during the first 24 weeks based on the standard of care for the target patient population with progressive advanced disease. Efficacy assessments will be every 12 weeks after the first 24 weeks. Additional safety precautions will include monitoring for potential hematologic toxicities by evaluating complete blood counts every 2 weeks through week 9, every 4 weeks through week 25, and then every 8 weeks thereafter during treatment. Prolonged myelosuppression will be monitored closely and diagnoses of myelodysplastic syndrome and acute myeloid leukemia occurring during or after study drug treatment will be reported. The potential for liver toxicity will be monitored by periodic transaminase testing with predefined dose modification and discontinuation criteria. Finally, patients with moderate renal impairment will receive talazoparib at a lower starting dose as they are at risk of higher exposure due to decreased renal clearance.

Talazoparib 1 mg/day was determined to be the maximum tolerated dose (MTD) and recommended phase 2 monotherapy dose based on the results of the phase 1, dose-escalation study in patients with solid tumors, PRP-001. Based on population PK analyses, talazoparib CL/F was estimated to be 37.1% lower in patients with moderate renal impairment than in those with normal renal function, resulting in higher exposure (Section 1.3.3). Simulations were performed to predict the steady-state exposure (AUC) for a 0.75 mg/day dose in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2) and for a 1 mg/day dose in patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) (Table 7). The predicted exposure at 0.75 mg/day for patients with moderate renal impairment is comparable to the exposure at 1 mg/day for patients with normal renal function as assessed by steady-state AUC. Based on these data, the planned starting dose for patients with moderate renal impairment is 0.75 mg/day. Patient with moderate renal impairment should remain on a reduced talazoparib dose throughout the study; dose escalation to a dose of 1 mg/day is not permitted for those patients.

Table 7. Predicted Talazoparib Mean Exposure at Steady-State

Renal Function	Dose (mg/day)	Steady-State AUC_{0-24} (ng•h/mL) Mean (5^{th}-95^{th} Percentile)
Normal	1	161 (136-188)
Moderate impairment	0.75	179 (163-196)

AUC_{0-24}, area under the plasma concentration-time curve from time zero to the time 24 hours (dosing interval).

4. PATIENT ELIGIBILITY CRITERIA

Selection of Study Population

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

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.

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Patients must be at least 18 years of age, and there must be evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

2. Histologically or cytologically confirmed adenocarcinoma of the prostate without signet cell, or small cell features. Histologic confirmation may be based on a de novo tumor biopsy obtained for purposes of screening. Biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel may not be performed for the sole purpose of determining study eligibility.

3. Patients must have measurable soft tissue disease per RECIST 1.1.

4. DNA damage repair gene alterations likely to sensitize to PARP inhibition (DDR-positive) as determined by:

   - Prospective testing of de novo or archival tumor tissue (via central laboratory) or prior historical (with sponsor preapproval) testing of tumor tissue using the Foundation Medicine, FoundationOne CDx™ NGS gene panel test;

     (Available archival or de novo tumor tissue also should be submitted prior to Day 1 to support concordance analyses and additional molecular profiling).

5. Unless prohibited by local regulations or ethics committee (EC) decision, consent to a saliva sample collection for retrospective sequencing of DDR genes used to assess patient eligibility based on tumor tissue, and to serve as a germline control in identifying tumor mutations.

6. Serum testosterone ≤1.73 nmol/L (50 ng/dL) at screening by central laboratory.

7. Bilateral orchiectomy or ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) agonist/antagonist (surgical or medical castration).

8. Progressive disease at study entry defined as 1 or more of the following 3 criteria:

   - A minimum of 3 rising PSA values with an interval of at least 1 week between determinations. The screening central laboratory PSA value must be ≥2 µg/L (2 ng/mL) if qualifying solely by PSA progression. For additional guidance, refer to Section 7.2.1.

   - Soft tissue disease progression as defined by RECIST 1.1.

   - Bone disease progression defined by PCWG3 with 2 or more new metastatic lesions on bone scan.

9. Metastatic disease. Patients whose only evidence of metastasis is measurable soft tissue disease below the aortic bifurcation will be acceptable. Neither bone metastases on bone scan nor non- measurable soft tissue disease alone will qualify a patient.

10. Previous treatment with 1 or 2 chemotherapy regimens including at least 1 taxane-based regimen for metastatic (non-castrate or castrate) prostate cancer. Patients may have received radium-223 and/or cabazitaxel, or were deemed unsuitable, declined, or did not have access to these therapies.

11. Documented disease progression (either radiographic or biochemical) on at least 1 novel hormonal therapy (enzalutamide and/or abiraterone acetate/prednisone) for the treatment of metastatic CRPC, irrespective of prior NHT treatment for non-castrate prostate cancer or nonmetastatic (M0) CRPC.

12. Bisphosphonate or denosumab dosage must have been stable for at least 4 weeks before day 1 for patients receiving these therapies.

13. ECOG performance status of 0 to 2.

14. Estimated life expectancy of ≥6 months as assessed by the investigator.

15. Able to swallow the study drug, have no known intolerance to study drugs or excipients, and comply with study requirements.

16. Must use a condom when having sex with a pregnant woman from the time of the first dose of study drug through 4 months after last dose of study drug. A highly effective form of contraception (Section 4.3.1) must be used from the time of the first dose of study drug through 4 months after last dose of study drug when having sex with a non-pregnant female partner of childbearing potential.

17. Must agree not to donate sperm from the first dose of study drug to 4 months after the last dose of study drug.

18. Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Use of systemic chemotherapeutic (including but not limited to taxanes), hormonal, biologic, or radionuclide therapy for treatment of metastatic prostate cancer (other than approved bone-targeting agents and GnRH agonist/antagonist) or any other investigational agent within 4 weeks before day 1.

2. Prior treatment with a PARP inhibitor, cyclophosphamide, or mitoxantrone chemotherapy. Patients who discontinued prior platinum-based chemotherapy ≤6 months prior to screening or whose disease previously progressed on platinum-based therapy at any time in the past are also excluded.

3. Treatment with any concurrent cytotoxic chemotherapy or investigational drug(s) within 4 weeks before Day 1 and/or during study participation.

4. Radiation therapy within 3 weeks (within 2 weeks, if single fraction of radiotherapy) before day 1.

5. Major surgery within 2 weeks before day 1.

6. Clinically significant cardiovascular disease, including any of the following:

    - Myocardial infarction or symptomatic cardiac ischemia within 6 months before screening;

    - Congestive heart failure New York Heart Association class III or IV;

    - History of clinically significant ventricular arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsade de pointes) within 1 year before screening;

    - History of Mobitz II second degree or third degree heart block unless a permanent pacemaker is in place;

    - Hypotension as indicated by systolic blood pressure <86 mm Hg at screening;

    - Bradycardia as indicated by a heart rate of <45 beats per minute on the screening electrocardiogram;

    - Uncontrolled hypertension as indicated by systolic blood pressure >170 mm Hg or diastolic blood pressure >105 mm Hg at screening.

7. Significant organ dysfunction by central laboratory results as defined by any one of the following laboratory abnormalities:

    - Renal: eGFR <30 mL/min /1.73 m^2 by the MDRD equation (Modification of Diet in Renal Disease [available via www.mdrd.com]).

    - Hepatic:

        - 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 metastasis, then AST or ALT ≥5 × ULN);

        - Albumin <2.8 g/dL.

- Bone marrow reserve: absolute neutrophil count <1500/µL, platelets <100,000/µL, or hemoglobin <9 g/dL (NOTE: may not have received growth factors or blood transfusions within 14 days before obtaining the hematology values at screening per central laboratory).

8. Known or suspected brain metastasis or active leptomeningeal disease.

9. Symptomatic or impending spinal cord compression or cauda equina syndrome.

10. Prior diagnosis of myelodysplastic syndrome or acute myeloid leukemia.

11. History of another cancer within 3 years before enrollment with the exception of nonmelanoma skin cancers, or American Joint Committee on Cancer stage 0 or stage 1 cancer that has a remote probability of recurrence in the opinion of the investigator and the sponsor.

12. Gastrointestinal disorder affecting absorption.

13. Current or anticipated use within 7 days prior to first dose of study drug or anticipated use during the study of strong P-gp inhibitors. For a list of strong P-gp inhibitors, refer to Section 5.11.

14. Any other acute or chronic medical or psychiatric condition (concurrent disease, infection, or comorbidity) that interferes with ability to participate in the study, causes undue risk, or complicates the interpretation of data, in the opinion of the investigator or sponsor, including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

15. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

16. Fertile male subjects who are unwilling or unable to use a condom as well as a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 4 months after the last dose of investigational product.

4.3. Lifestyle Requirements

4.3.1. Contraception

All fertile male subjects who are, in the opinion of the investigator, sexually active, capable of ejaculation and/or at risk for pregnancy with their partner(s) must agree to use both a condom as well as a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 4 months after the last dose of

investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects capable of ejaculating must agree to prevent potential transfer to and exposure of fetus/partner(s) to drug through ejaculate (even after vasectomy) by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 4 months after the last dose of investigational product. All fertile males must agree not to donate sperm from the first dose of study drug to 4 months after the last dose of study drug.

If applicable, as indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). If applicable, sperm donation and fetus/partner exposure should also be discussed as per schedule of activities. In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy or fetus/ partner exposure is known or suspected.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

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

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product, or study drug, is talazoparib. The sponsor will provide talazoparib capsules.

5.1. Allocation to Treatment

This is an open-label study in which all eligible subjects will receive talazoparib. The study will use an interactive response technology (IRT) system (interactive Web-based response system [IWRS]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a subject identification number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

5.2. 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 pharmacy binder.

5.3. 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 and storage, clinical trial statement, sponsor name, batch/lot number, and product retest or expiration date.

5.4. Storage of Talazoparib

The drug product should be stored safely and properly in accordance with the study drug label. Specific details describing storage conditions may be found in the Investigational Product Manual.

5.5. Directions for Administration of Talazoparib

The daily dose of talazoparib is 1 mg/day given orally at approximately the same time each day. The starting and maximum dose will be 0.75 mg/day for patients with moderate renal impairment at screening (eGFR: 30-59 mL/min/1.73 m^2 per central laboratory).

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.

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

Dose modifications due to adverse events are described below.

5.6. Dose Modifications

5.6.1. Dose Modifications Due to Adverse Events

Dose modifications for talazoparib due to adverse events are described in Table 8:

Table 8. Talazoparib Dose Modifications Due to Adverse Events

Toxicity	Management of Adverse Events [1]
Grade 1 or 2	No requirement for dose interruption or dose reduction.
Selected hematologic grade 3 or 4 events	
Grade 3 or 4 Anemia (hemoglobin <8.0 g/dL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL or better, then resume talazoparib at a reduced dose per Figure 3. If anemia with hemoglobin <8.0 g/dL recurs after dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL then resume talazoparib at a further reduced dose per Figure 3. If anemia persists for >4 weeks without recovery of hemoglobin to at least 9.0 g/dL despite supportive care measures at any dose level, discontinue talazoparib and consider referral to a hematologist. Transfusions and other supportive measures are permitted to support management of hematological toxicities at any occurrence.
Grade 3 or 4 Neutropenia (ANC <1000/µL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/µL, then resume talazoparib at a reduced dose as per Figure 3. If neutropenia recurs after the dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/µL, then resume talazoparib at a further reduced dose. If neutropenia persists for >4 weeks without recovery to ≥1500/µL at any dose despite supportive care measures, discontinue talazoparib and consider referral to a hematologist. G-CSF and GM-CSF may be used at investigator's discretion for the supportive treatment of neutropenia at any occurrence.
Grade 3 or 4 Thrombocytopenia (platelets <50,000/µL)	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥50,000/µL then resume talazoparib at a reduced dose per Figure 3. If thrombocytopenia (<50,000/µL) recurs after one dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥75,000/µL, then resume talazoparib at a further reduced dose. If thrombocytopenia persists for >4 weeks without recovery to ≥50,000/µL despite supportive care measures, discontinue talazoparib and consider referral to a hematologist. Thrombopoietin analogues and/or platelet transfusions may be used at investigator's discretion for the supportive treatment of thrombocytopenia at any occurrence.

Table 8. Talazoparib Dose Modifications Due to Adverse Events

Toxicity	Management of Adverse Events [1]
Nonhematologic laboratory grade ≥3 events, except abnormal liver tests[1]	Hold talazoparib as follows: For clinically significant Grade 3 laboratory abnormalities hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Resume talazoparib at the same dose or reduce by 1 dose level per Figure 3. If Grade 3 laboratory abnormality recurs, hold talazoparib until the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases). Reduce talazoparib one dose level per Figure 3. For Grade 4 laboratory abnormalities, hold talazoparib. Resume talazoparib when the laboratory abnormality resolves to Grade ≤2 (to baseline grade for creatinine increases) at a 1 dose level reduction per Figure 3. Talazoparib must be discontinued if a Grade 4 adverse event recurs after treatment resumes. Implement supportive care per local guidelines. Contact sponsor to discuss potential dose modification. Talazoparib must be permanently discontinued for unresolved Grade 3 toxicity lasting longer than 14 days or for Grade 4 toxicity lasting longer than 3 days. Treatment may be resumed at a 1 dose level reduction if clear clinical benefit is observed, after discussion with the sponsor.
Grade ≥3 abnormal liver tests	Subjects who develop abnormal liver tests (AST, ALT, total bilirubin [TBili]), signs or symptoms consistent with hepatitis during study treatment may meet the criteria for temporarily withholding or permanently discontinuing study drug talazoparib. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities if any of the following occur: • Subjects who develop AST or ALT >5 x ULN (without TBili >2 x ULN); OR • Subjects with baseline total bilirubin <1.5 x ULN who subsequently present with >3 x ULN; OR • Subjects with baseline total bilirubin >1.5 x ULN and <3 x ULN (eg, Gilberts) who subsequently present with bilirubin >5 x ULN. If abnormalities resolve to baseline values within 2 weeks, there are no signs of drug induced liver injury (DILI), and none of the permanent discontinuation criteria are met, then upon discussion with the Sponsor, the investigator may re-challenge at a reduced dose level. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities if any of the following occur: • Refer to Section 8.4.2 for potential DILI cases; • Subjects with AST/ALT >5 × ULN that persists for more than 7 days (AST/ALT >8 × ULN for subjects with hepatic involvement); • Subjects with AST/ALT >20 × ULN that persists for longer than 3 days. • Subjects with Tbili >3 × ULN that persists for longer than 7 days (>5 × ULN for subjects with Gilbert's disease).

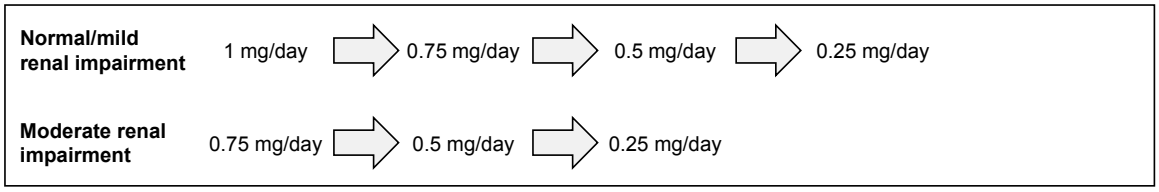
Table 8. Talazoparib Dose Modifications Due to Adverse Events

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

1. Talazoparib dose re-escalation may be allowed after the reduced dose is tolerated without recurrence of toxicities, and after discussion with the sponsor. AML, acute myeloid leukemia; ANC, absolute neutrophil count; MDS, myelodysplastic syndrome.

The dose of talazoparib may be reduced incrementally as shown in Figure 3:

Figure 3. Talazoparib Dose Reduction for Toxicity



Dose re-escalation: Dose re-escalation may be allowed after toxicities resolve, the reduced dose has been tolerated, and after discussion with the sponsor.

5.7. Treatment Compliance

Accountability for the study drug capsules will be performed to document compliance with the dosing regimens. Patients will be asked to bring all used and unused study drug bottles to study visits for personnel to perform drug accountability prior to dispensing additional study drug. Study site personnel must make reasonable efforts to obtain used and unused study drug bottles from patients who do not routinely return them at study site visits. Unreturned capsules will be considered to have been taken.

5.8. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all talazoparib is stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the talazoparib Investigator's Brochure will be superseded by the storage conditions stated on the label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take home investigational products.

Refer to the Investigational Product Manual for additional guidance on storage conditions and actions to be taken when conditions are outside of the prespecified range.

5.9. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All bottles of study drug must be returned to the investigator by the patient at every visit and at the end-of-treatment visit. Patients who do not return bottles at the end-of-treatment visit will be reminded to bring them at their next visit.

5.9.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.10. Concomitant Treatment(s)

Concomitant medications will be assessed at all clinic visits. 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. All prior cancer treatments, other medications taken within 28 days before day 1, 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.

Required and prohibited medications are described in Table 9. Supportive medications may be provided prophylactically or therapeutically per investigator discretion. Concomitant use of steroids as hormonal treatment for prostate cancer is not allowed. Intranasal, inhaled, or topical corticosteroids are allowed. Palliative low dose treatment with corticosteroids (10 mg or less of prednisone or equivalent/day) to reduce pain and inflammation although allowed, if no alternative therapy is available, is discouraged; investigators are to document in the case report form (CRF) the reason why steroids were given. Higher doses of steroids should be avoided unless no other therapies are available. Deviation from these guidelines should occur only if absolutely necessary for the well-being of the patient, and the sponsor is to be notified to determine whether continued treatment with study drug is permitted.

Study drug must be permanently discontinued upon initiation of a prohibited antineoplastic or investigational therapy. Patients who discontinue treatment due to initiation of such therapy will complete safety follow-up per Section 6.5 and will have long-term follow-up per Section 6.6. Patients will use analgesic logs (Appendix 5) to document their use of any and all analgesics for prostate cancer pain beginning 7 days before a scheduled visit (or scheduled contact during the post-treatment follow-up periods). Analgesics include but are not limited to opioids, and nonopioid analgesics, which include acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and ketorolac, and selective cyclooxygenase type 2 (COX-2) inhibitors, such as celecoxib and rofecoxib.

Table 9. Instructions for Use of Concomitant Therapies

Use Category	Medication or Treatment	Comment on Use
Required	Ongoing androgen deprivation therapy with a GnRH agonist/antagonist or bilateral orchiectomy (medical or surgical castration).	For the duration of the study.
Prohibited	Prior PARP inhibitor, cyclophosphamide, or mitoxantrone ever in the past; also, prior platinum within the 6 months prior to screening or if there was ever prior disease progression on platinum.	Prior to screening and through safety follow-up.
	Any systemic (eg, chemotherapeutic, hormonal, biologic, radionuclide) antineoplastic therapy, and other investigational agents.	Within 4 weeks before day 1 through safety follow-up.
	Radiation therapy.	Within 3 weeks (within 2 weeks, if single fraction) before day 1.
	P-gp inhibitors (refer to Section 5.11).	For the duration of the study.
Used with caution	Transporter inhibitors (refer to Section 5.11).	For the duration of the study.

GnRH, gonadotropin-releasing hormone; PARP, poly(ADP-ribose) polymerase.

5.11. Potential Interactions Between the Test Product and Concomitant Medication

- Strong P-gp inhibitors that result in ≥2-fold increase in the exposure of an in vivo probe P-gp substrate according to the University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/) are prohibited: amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, verapamil and valspodar.

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

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

5.12. Rescue/Salvage Medication

New treatments for prostate cancer prior to the determination of radiographic progression by the independent blinded reviewers are strongly discouraged.

6. STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The study periods will include prescreening (optional), screening, treatment, safety follow-up, and long-term follow-up. The timing of all study procedures is provided in the schedules of activities (Table 1, Table 2, Table 3, Table 4). The interactive response system user manual contains the information needed for registering patient status (eg, assigning screening numbers, indicating screen failure, and end of treatment).

6.1. Prescreening (optional)

Certain procedures or activities may be performed during a prescreening period defined as any time before a prospective study participant signs an informed consent form to be formally screened for study enrollment. These include a biopsy procedure to obtain de novo tumor tissue or the retrieval of archived tumor tissue for evaluation of a DNA damage repair deficiency as assessed using the FoundationOne CDx™ (Foundation Medicine) gene mutation panel. CCI [redacted]

A separate prescreening consent form must be signed if de novo or archival tissue and blood sample will be obtained and analyzed before the patient signs consent for the protocol screening period. In addition, after the prescreening consent is signed, previously obtained (ie, historic) testing results from analysis of tumor tissue using the FoundationOne CDx™ test may be submitted.

Test results obtained using the FoundationOne CDx™ test identifying DNA repair deficiencies likely to sensitize to PARP inhibition may be considered for eligibility with sponsor approval. If sufficient residual DNA is available at Foundation Medicine, this could be used to confirm a patient's eligibility for enrollment. Note that if eligibility for enrollment is established based either on historical results or residual DNA testing, available archival or de novo tumor tissue also should be submitted prior to Day 1.

Study site personnel must document the informed consent process for tissue and blood sampling in the patient's clinical record. After obtaining signed informed consent, study site personnel will access the interactive response system to assign a screening identification (ID) number for each potential study participant. In addition, the demographic data case report form (CRF), the Prior Anti-Cancer Therapies CRF and the Medical History- Prostate Cancer CRF should be completed at pre-screening if pre-screening is performed. For subjects for whom new tissue or blood sampling needs to be obtained and as applicable, AEs and/or research related injuries are to be reported as per Section 8.4.5.

Prescreening procedures are listed in the schedule of activities in Table 1.

6.2. Screening Period

The screening period will be from day -28 through day-1 for most procedures (Table 2). For the purposes of this study, there will be no day 0.

6.2.1. Informed Consent

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 and dated informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care, and must document the informed consent process in the patient's source documents.

6.2.2. Screening Identification Numbers

After obtaining signed informed consent, study site personnel will access the interactive response system to assign a screening ID number (if not obtained previously during prescreening) for each potential study participant.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent, study site personnel will document the screen failure or consent withdrawal in the patient's source documents. The documentation will include demographics (which may have been assessed at pre-screening), and medical history for prostate cancer, prior treatment(s) for prostate cancer, the reason for screen failure, the eligibility criteria reviewed, and procedures performed and, as applicable, any AE/SAE that occurs during the active collection period (refer to Section 8.1.4) until the patient is determined to be a screen failure.

6.2.3. Screening Procedures

Screening procedures are listed in the schedule of activities in Table 2. All procedures must be completed within 28 days before day 1 except as noted.

Scans obtained within 42 days before day 1 as part of standard of care may be used for the screening radiographic assessment.

De novo or archival tumor tissue for analysis of DNA damage repair deficiencies is required for enrollment (if not collected at prescreening) as assessed using the FoundationOne CDx™ (Foundation Medicine) gene mutation panel. In addition, previously obtained (ie, historic) testing results from analysis of tumor tissue using the FoundationOne CDx™ test may be submitted with sponsor approval. Should a patient qualify based either on prior results or DNA available at Foundation Medicine, available de novo or archival tumor tissue should be submitted prior to Day 1 to support planned concordance analysis CCI [redacted] The investigator will assess the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply.

After a patient is screened and the investigator determines the patient is eligible, study site personnel will complete an Enrollment Authorization Form and fax or email it to the sponsor or designee to approve the enrollment in writing. Eligibility will be determined as per the amendment approved at the site at the time the Enrollment Authorization Form is reviewed. No eligibility waivers will be granted.

6.3. Treatment Period

6.3.1. Treatment Period Visit Windows

All treatment period visits have a visit window of ±3 days (ie, 3 days before or after the given day), except the day 1 visit (start of study treatment). The window for imaging assessments is ±7 days.

CCI [redacted]

Study drug supplies must be taken into account when scheduling visits. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

6.3.2. Treatment Period Procedures

Specified study procedures will be performed at each clinic visit according to the schedule of activities (Table 3).

- All patients will have clinic visits every 2 weeks for the first 8 weeks (through week 9), then every 4 weeks through week 25, and every 12 weeks thereafter.
- Day 1 is the day of the first dose of study drug treatment (talazoparib). Questionnaires should be completed CCI [redacted]
- Safety assessment labs will be done by the central laboratory per schedule of assessment. In addition, every effort should be taken to send unscheduled samples to the central laboratory to monitor resolution of AE/SAE. Pretreatment serum chemistry and hematology laboratory tests may be performed at the local laboratory within 3 days before the scheduled times (every 2 weeks through week 9, then every 4 weeks through week 25, and every 8 weeks thereafter). The investigator must review the laboratory results before dosing. Regardless of whether local laboratory testing is obtained for serum chemistry and hematology values, blood samples must be sent to the central laboratory for evaluation. Results from local laboratory assessments will be entered in the appropriate CRF.

- Radiographic assessments will be obtained and submitted for independent central review (Section 7.1.2).

- Patients will document their pain symptoms and their use of any and all analgesics for prostate cancer pain by completing both the pain log and an analgesic log during each of the 7 consecutive days preceding a scheduled visit after Day 1.

- Any diagnosis of myelodysplastic syndrome (MDS) or AML will be reported as an SAE (Section 8.2.3). If requested, provide tissue samples and other supporting data used to enable diagnosis for review by blinded independent reviewers.

Study visits and study drug treatment will continue until criteria for permanent study discontinuation are met (Section 6.4). PSA progression or CTC count increases alone should not lead to study drug discontinuation.

6.3.3. Unscheduled Visit Procedures

Unscheduled visits/assessments may be performed anytime to assess or follow up adverse events, to perform scans, or at the request of the patient or investigator or sponsor, or to account for any insufficient, inadequate, or missed sample or assessments. 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 or for suspected disease progression, diagnostic tests may be performed based on investigator assessment as appropriate. Imaging may be performed if appropriate for patients who are symptomatic or for whom radiographic progression or response is being determined. All radiographic assessments obtained (including unscheduled ones) will need to be submitted for independent central review. Unscheduled visits and visit procedures are listed in Table 3. Other study procedures may be performed as clinically appropriate.

6.4. Permanent Treatment Discontinuation

Treatment discontinuation is defined as permanent cessation of study drug treatment administration. After permanent discontinuation, safety follow-up will occur per Section 6.5, 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 10.

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also Section 8.1.3 Withdrawal From the Study Due to Adverse Events) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient.

In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved adverse events (AEs). If applicable, patients who return for a final visit will undergo safety and long term follow-up procedures as shown in Table 3 and Table 4.

Patients may withdraw from the study at any time at their own request. If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. If allowed by local laws and regulations survival information will be collected using public records.

Table 10. Primary Reasons for Permanent Treatment Discontinuation

Reason	Comment
Radiographic progression	Per RECIST 1.1 for soft tissue disease and per PCWG3 for bone disease. Must be determined by independent central review and confirmed for bone disease progression. Refer to Section 7.1.2.
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 8.4.2] or MDS/AML]). Refer to Section 8. May or may not be related to disease progression.
Administration of any systemic anticancer therapy	Refer to Section 5.10.
Patient decision	Patients may permanently discontinue treatment anytime for any reason. Withdrawal of consent for study treatment should be distinguished from withdrawal of consent for further participation in the study, including follow-up. This category should be selected if adverse event, disease progression, or administration of prohibited concomitant therapy does not apply. Patients are strongly encouraged to continue in long-term follow-up as described in Section 6.6, even if they choose to permanently discontinue study drug treatment.

Table 10. Primary Reasons for Permanent Treatment Discontinuation

Reason	Comment
Investigator decision	Protocol treatment may be discontinued if the investigator considers it is in the patient's best interest. This category should be selected if adverse event, disease progression, or administration of prohibited concomitant therapy does not apply and the patient preferred to continue treatment.
Major noncompliance with protocol	The sponsor or investigator may request permanent treatment discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance.
Lost to follow-up	Refer to Section 6.7.
Sponsor discontinuation of study	The sponsor reserves the right to terminate the study anytime for any reason as described in Section 14. The sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.

6.5. Safety Follow-up

Patients will have safety follow-up after permanent discontinuation of study drug treatment. Safety follow-up should occur approximately 28 days after the last dose of study drug or before initiation of new antineoplastic or investigational therapy, whichever occurs first. In the event that new antineoplastic or new investigational therapy is initiated before safety follow-up occurs (eg, a physician not associated with protocol C3441006 (MDV3800-06) initiates the treatment, and study site personnel are not aware of the treatment until afterward), safety follow-up should be scheduled as soon as possible.

Safety follow-up procedures are listed in Table 3.

If treatment is discontinued due to an adverse event or serious adverse event, the event(s) must be followed up as described in Table 3.

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 28 days after the last dose of study drug or before initiation of new antineoplastic or new investigational therapy, whichever occurs first. If the patient does not respond to telephone calls, the procedures for lost to follow-up in Section 6.7 should be followed.

6.6. Long Term Follow up

For long-term follow-up procedures see Table 4. This period begins after safety follow-up and can be conducted by telephone unless imaging is required. Long-term follow-up begins after safety follow-up and continues until the patient dies, withdraws consent or, refuses follow up, or the study is terminated. Radiographic imaging should continue during long-term follow-up for patients who discontinue study drug for any reason other than radiographic progression, determined by independent central review, when the patient has not withdrawn consent for follow-up. All known follow-up anticancer therapies have to be entered in the CRF. Potential cases of AML or MDS will be entered in the CRF and reported as SAEs in the sponsor safety database irrespective of investigator's opinion of causality or time of diagnosis.

6.7. Lost 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. Survival information will be collected from public records if allowed by local laws and regulations.

7. ASSESSMENTS

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

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

CT scans/MRI/bone scans will be reviewed by independent radiologists (central review). The purpose of this review is to evaluate images for appropriate study endpoints. Central image review is not a complete medical review of the participant and no incidental findings will be shared with the principal investigator (PI), site staff, or the participant. All safety reviews will be the sole responsibility of site staff.

7.1. Assessment of Efficacy

7.1.1. Assessment of Primary Efficacy Endpoint: ORR

The primary efficacy endpoint is best ORR and the assessment uses standard radiographic methods to evaluate response for soft tissue disease.

7.1.2. Assessment of Radiographic Response and Progression

Disease status will be assessed at regular intervals during the course of the study by CT (chest, abdomen, pelvis), which is the preferred method, or MRI (abdomen, pelvis) of soft tissue, and CT of the chest without contrast if the patient is allergic to CT contrast agents, and whole body radionuclide bone scan. The radiographic assessment of soft tissue disease (including soft tissue components of lytic or mixed bone lesions) will use RECIST 1.1 (Eisenhauer et al, 2009), and bone disease will be evaluated per PCWG3 (Scher et al, 2016), with confirmatory imaging requirements shown in Table 11 (modified RECIST1.1/PCWG3). The determinations for study endpoints will be made by independent central review. However, investigator assessments will be collected in the CRF.

Table 11. Confirmatory Imaging Requirements for Soft Tissue per RECIST 1.1 and Bone per PCWG3

Disease Site	Response	Progression
Soft tissue	Must be confirmed at least 4 weeks later[1]	No confirmation required[1,2]
Bone	Not applicable	Must be confirmed at least 6 weeks later[1,2]

1. For analytic purposes.
2. To inform permanent treatment discontinuation.

PCWG3, Prostate Cancer Working Group 3; RECIST 1 1, Response Evaluation Criteria in Solid Tumors, version 1.1.

An objective response is defined as a best overall response of CR or PR per RECIST 1.1 by independent central review. Responses must be confirmed by a follow-up CT or MRI at least 4 weeks later and with no evidence of confirmed bone disease progression per Prostate Cancer Working Group 3 (PCWG3) criteria on repeat bone scan at least 6 weeks later by independent central review.

Radiographic assessments will be every 8 weeks through the first 24 weeks, then every 12 weeks thereafter. Scans may be obtained sooner than scheduled if disease progression is clinically suspected (for example, PSA progression). The study films (CT/MRI and bone scan) will be sent for independent central review.

The documentation required for the determination of radiographic progression is shown in Table 12.

Table 12. Criteria for Evidence of Radiographic Progression

Date Progression Detected (Visit)[1]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan
Week 9	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3.	Timing: at least 6 weeks after progression identified or at week 17 visit.[2]	Persistence of at least two of the lesions seen at week 9 AND 2 or more additional new bone lesions on bone scan compared to week 9 scan (2+2 rule). Date of progression is the date of the first post treatment scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	No confirmatory scan required for soft tissue disease progression.
Week 17 or later	Bone lesions: 2 or more new lesions on bone scan compared to week 9 bone scan.	Timing: at least 6 weeks after progression identified or at next imaging time point.[2]	At least 2 of the lesions first identified as new compared to week 9 must be still present. Date of progression is the date of the scan that first documented 2 or more new lesions.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	No confirmatory scan required for soft tissue disease progression.

1. Progression detected by bone scan at an unscheduled visit either before week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
2. Confirmation must occur at the next available scan.

CT, computed tomography; MRI, magnetic resonance imaging; PCWG3, Prostate Cancer Working Group 3; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

7.2. Assessments of Secondary Efficacy Endpoints

The secondary efficacy endpoints include time to objective response, duration of response, proportion of patients with PSA response ≥50%, proportion of patients with conversion of CTC count, time to PSA progression, radiographic PFS, overall survival. The study assessments of efficacy for these endpoints will include standard radiographic and imaging methods to evaluate disease progression and response, PSA, survival status monitoring, pain and quality of life questionnaires, and CTC enumeration.

7.2.1. Assessment of PSA

Local laboratory PSA values will be used to determine eligibility for the study at screening (Table 2) including a minimum of 3 consecutive, rising PSA values with an interval of at least 1 week between determinations; values are to be recorded on the CRF. The third PSA may or may not be the central lab screening PSA. (If the screening central lab PSA is lower than local lab PSA #2, then a third local lab PSA may be submitted instead if the PSA measurement is higher than the second local lab PSA.)

A central PSA assessment will be done at screening for all patients.

The screening value must be ≥2 ng/mL as assessed at the central laboratory if qualifying solely based on PSA progression. During the study, PSA will be measured at the central laboratory according to the schedule of activities (Table 3). PSA progression alone should not lead to study drug discontinuation, and study drug administration should continue regardless of PSA increases until radiographic progression is determined by independent central review. PSA progression or response, as determined by the central lab, must be confirmed at least 21 days later.

7.2.2. Assessment of Survival

The survival status of each patient will be monitored during study treatment and after permanent treatment discontinuation for any reason. Survival status will be documented during long-term follow-up according to the schedule of activities (Table 4). The date and cause of death will be recorded. During the course of the study, the sponsor may request that a survival sweep be conducted to obtain an accurate number of deaths across the study. The sponsor will provide instructions on these survival sweeps immediately before they commence as well as a timeline for contacting patients.

7.2.3. Assessment of Circulating Tumor Cells

The assessment of CTCs will be performed by collecting blood samples according to the schedule of activities (Table 3). CTC count increases alone should not lead to study drug discontinuation. Details on sample handling and shipping will be provided separately in a laboratory manual.

7.2.4. Assessment of Patient Reported Pain

The assessment of pain will use the BPI-SF. This questionnaire is a validated instrument that uses a self-reported scale assessing level of pain, its effect on activities of daily living, and analgesic medication use. This study will use the short form containing 9 main questions related to pain. The primary question (paraphrased) is "On a scale of 0 to 10, please rate your pain at its worst in the last 24 hours." The questionnaire is provided in Appendix 2. It is important that patients are fluent in reading the language used in the questionnaire and that they complete it without influence of the investigator, study site staff, or anyone else.

Tracking analgesic use is particularly important to ensure that the delay in pain progression observed is truly the result of the treatment being studied rather than the result of an increase in analgesic use. After the Day 1 visit, pain (assessed using BPI-SF question 3, Appendix 4) and analgesic use (assessed using an analgesic log, Appendix 5) will be collected for each of 7 consecutive days prior to study visits; the timing of collection is shown in Table 3 and described in Section 6.3.

7.2.5. Assessment of Patient-Reported General Health Status

The assessment of this patient-reported outcome will use the EQ-5D-5L. The EQ-5D-5L questionnaire is a standardized instrument that measures health-related quality of life for men with prostate cancer. Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale to self-rate general health state on a scale from "the worst health you can imagine" to "the best health you can imagine." The EQ-5D-5L questionnaire is provided in Appendix 3.

On Day 1, patients will complete these questionnaires before the first dose of study drug. At subsequent visits, patients will complete these questionnaires at the site before any other study activities and in the same order at each visit. These questionnaires will be collected according to the schedule of assessments in Section 6.3.

7.3. Assessments of Safety

The assessment of safety will include adverse events, physical examinations, vital signs, and clinical laboratory tests. AE will be graded using CTCAE version 4.03. 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 7.3.1, and for physical examinations and vital signs in Section 7.3.2.

7.3.1. Clinical Laboratory Tests

Routine clinical laboratory tests (hematology, serum chemistry) will be performed according to the schedules of activities by the central laboratory (Table 2, Table 3). Central safety laboratory assessments may also be collected as unplanned, at the investigator's discretion, or to monitor adverse events or determine if dosing modifications are required. Local safety laboratory assessments may also be performed but should not replace central lab assessments; results from local laboratory assessments are to be entered in the appropriate CRF. Every effort should be taken to collect samples for central laboratory safety assessments even if unplanned. 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 below. All samples for laboratory analysis must be collected, prepared, labeled, and shipped according to laboratory requirements.

All clinical laboratory tests will be performed by the central laboratory specified in Form FDA 1572 Section 4 unless otherwise specified. The central laboratory reference ranges will be used. Eligibility at screening will be based on central laboratory assessments (preceding local laboratory PSA values will also be required if qualifying based solely on PSA progression). The screening value must be ≥2 ng/mL as assessed at the central laboratory if qualifying solely based on PSA progression.

A local clinical laboratory may be used to evaluate serum chemistry and hematology within 3 days before a scheduled visit. The results of these local laboratory assessments may be used for dosing decisions. However, samples must also be collected and sent to the central laboratory for testing.

For all patients, a local clinical laboratory may be used to assess samples at unscheduled visits or for urgent care to evaluate an adverse event. Central laboratory samples should also be obtained whenever possible during unscheduled visits.

Central Laboratory Tests

Hematology	Chemistry	Additional
Hematocrit	Albumin	PSA (prostate-specific antigen)
Hemoglobin	Total protein	Testosterone (screening only)
Mean corpuscular volume	Alkaline phosphatase	
Red blood cell count	ALT (alanine aminotransferase)	
Platelet count	AST (aspartate aminotransferase)	
	Total bilirubin	
White blood cell count with differential	Blood urea nitrogen	
	Creatinine	
Total neutrophils	Glucose (nonfasting)	
Lymphocytes	Bicarbonate	
Monocytes	Calcium*	
Eosinophils	Chloride	
Basophils	Magnesium	
	Phosphate	
	Potassium	
	Sodium	
	LDH (lactate dehydrogenase)	

The laboratory manual for this study provides details regarding sample collection procedures, laboratory tests, and additional tests that may be required. *Central lab data include calcium and calcium albumin corrected.

7.3.2. Physical Examinations, Vital Signs, and ECGs

The investigator will perform physical examinations according to the schedules of activities (Table 2, Table 3). Interval medical history will be reviewed as a part of physical examinations. Physical examinations will 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. Weight will be measured at the time of the examination. Height will be measured only at screening. Vital sign measurements will include blood pressure, heart rate, and temperature.

12-Lead ECGs will be obtained and read locally at screening. Additional ECGs may be obtained as necessary per standard of care.

7.4. Pharmacokinetic Assessments

Blood samples will be collected predose and postdose according to the schedules of activities (Table 3). Additional PK blood samples may be collected from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation. Plasma talazoparib concentrations will be measured using a validated method.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time AND collected prior to administration of the investigational product on that day (for pre-dose PK samples) will be considered protocol compliant. Patients must be instructed to withhold their daily dose of study drugs on PK sampling days until the pre-dose PK sample collection has been completed. The actual time of the sample collection and the most recent dosing time before and after each collection will be recorded on the CRF. The date of missing dose should also be recorded in the CRF.

Samples will be collected, processed and shipped as described in the laboratory manual.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

7.7. Assessment of ECOG Performance Status

Assessment of ECOG performance status is required to assess patient functional status for study eligibility purposes and will be performed throughout the study according to the schedules of activities (Table 2, Table 3). Scoring for the assessment is shown in Table 13.

Table 13. ECOG Performance Status

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

Source: Oken et al, 1982
ECOG, Eastern Cooperative Oncology Group.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the 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	All
Non-serious AE	All	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)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) 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 on the AE page(s) of 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/legally acceptable representative. In addition, each study patient/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 or treatment 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 provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

A different reporting period applies only to patients who sign the molecular prescreening consent as described in Section 8.4.5.

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

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 as of signing of the main informed consent document (ICD) at screening.

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. All SAEs of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) are to be reported to Pfizer Safety irrespective of investigator's opinion of causality or time of diagnosis.

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 are recorded on the CRF.

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.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); 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.

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 only 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, version 4.03) 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

The investigator will use the following definitions of severity in accordance with the current CTCAE version (4.03) to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

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.

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

Although this study will be conducted exclusively in male patients, it is theoretically possible for female partners to be exposed to study drug during pregnancy. 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

In female partners of study patients, 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:
    - Overdose (any dose higher than the prescribed 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 as per local guidelines, and treat symptomatically;
    - 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, as prescribed, for 6 or more days (approximately <80%) within 4 weeks, unless dose was withheld due to an AE.
- 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 in a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor (study clinician) 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**.

8.4.5. Reporting AEs and/or Research-Related Injuries for Patients Who Sign the Molecular Prescreening Consent

*This section is applicable **only to those subjects for whom new tissue or blood sampling needs to be obtained at prescreening.** For these patients, there is an informed consent specifically for these procedures that is completely separate from the study informed consent.*

The investigator must obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a research-related injury requiring immediate notification to Pfizer as described below.

8.4.5.1. Adverse Events

Any AE that occurs from the time the patient undergoes a procedure to obtain de novo tissue or blood through and including 14 days upon completion of said procedure, must be recorded. The investigator is required to assess whether the AE may be related to the patient's participation in the study.

Record adverse events on the CRF from the time the patient undergoes a procedure to obtain tissue or blood through until 14 days after completion of said procedure.

8.4.5.2. Research-Related Injuries

Should a patient, in the investigator's opinion, suffer a medically important research-related injury caused by their participation in the study, the designated Pfizer clinician must be notified immediately.

A medically important research-related injury is any untoward medical occurrence 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.

Medical and scientific judgment is exercised in determining whether an injury 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 outcomes listed in the definition above, the important medical event should be reported as a research-related injury.

An investigator may be requested by the designated Pfizer clinician to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or 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 or its designated representative.

Record research-related injuries on the CRF from the time the patient undergoes a procedure until the patient is deemed a screen failure or until the end of the study.

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Statistical and Analysis Plans

The statistical methods and analyses for this study will be described in detail in the statistical analysis plan. Three analyses are planned, including an initial safety analysis/efficacy analysis followed by two efficacy analyses. The initial safety/efficacy analysis will be performed after 20 patients with measurable soft tissue disease and DDR deficiencies likely to sensitize to PARP inhibitor therapy have received the study drug for at least 8 weeks. Efficacy analyses of the primary endpoint will also be performed when 60 and 100 patients have completed at least 6 months of study treatment or are no longer being followed (ie, have withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up).

9.2. Analysis Populations

The DDR Deficient Measurable Disease population is defined as all enrolled patients who have measurable soft tissue disease at screening by ICR, have DDR deficiencies likely to sensitize to PARP inhibitor therapy and receive at least one dose of talazoparib. The DDR Deficient Measurable Disease population will be used for all baseline characteristics summaries and efficacy analyses.

Summaries and listings of efficacy and baseline data for patients that were enrolled under previous protocol versions and who are not part of the DDR Deficient Measurable Disease population will be described in the statistical analysis plan.

The safety population is defined as all patients who receive at least one dose of talazoparib. The safety population will be used for all safety analyses.

The PK population is defined as all patients from the safety analysis set who have at least 1 reportable drug concentration data point.

The PRO population is defined as all patients from the DDR Deficient Measurable Disease population who have completed a baseline and at least one post-baseline PRO assessment prior to the end of study treatment.

The CTC evaluable population is defined as all patients with a baseline CTC assessment and at least 1 post-baseline CTC assessment from the DDR Deficient Measurable Disease population.

CCI [redacted]

9.3. Efficacy Analyses

9.3.1. Primary Efficacy Analyses

The primary study objective is to evaluate efficacy as measured by the primary endpoint best ORR. The best ORR is defined as the proportion of patients with a best overall soft tissue response of CR or PR per RECIST 1.1 by independent central review. Soft tissue responses will be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated CT or MRI with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria by independent central review. ORR will be summarized along with the 95% CI using the Clopper-Pearson method (Clopper-Pearson; 1934). Analyses based on assessment by the investigator will also be performed.

9.3.2. Secondary Efficacy Analyses

The following efficacy parameters will be evaluated.

9.3.2.1. Time to Objective Response

The time from first dose of talazoparib to the first documented objective evidence of soft tissue response with no evidence of confirmed bone disease progression on bone scan per PCWG3. Soft tissue response is defined as a best overall response of CR or PR per RECIST 1.1 by independent central review. The response must be confirmed at least 4 weeks later with a repeated CT/MRI. Analyses will include the patients from the DDR Deficient Measurable Disease population who achieve a confirmed CR or PR without documentation of confirmed bone progression. Descriptive statistics (mean, standard deviation, median, minimum, maximum, and quartiles) will be provided. Analyses based on assessment by the investigator will also be performed.

9.3.2.2. Duration of Response

The duration of response is defined as the time from the first objective evidence of soft tissue response (subsequently confirmed) per RECIST 1.1 by independent central review and no evidence of confirmed bone disease progression per PCWG3 to the first subsequent objective evidence of radiographic progression or death due to any cause, whichever occurs first. Radiographic progression is defined as soft tissue progression per RECIST 1.1 by

independent central review or bone disease progression per PCWG3 by independent central review. Details on the conventions for censoring will be presented in the statistical analysis plan. Analyses will include the patients from the DDR Deficient Measurable Disease population who achieve a confirmed CR or PR without documentation of confirmed bone progression. Duration of response will be estimated using the Kaplan-Meier method and 95% CI for median time will be calculated using the Brookmeyer-Crowley method (Brookmeyer & Crowley, 1982). Analyses based on assessment by the investigator will also be performed.

9.3.2.3. Proportion of Patients With PSA Response ≥50%

PSA response will be calculated as a decline from baseline PSA (ng/mL) by at least 50% measured by central laboratory. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. Patients without a baseline and at least one post baseline PSA assessment will not be analyzed for this endpoint. Only assessments performed from the date of first dose of study treatment until confirmed PSA progression or start of new anticancer treatment given after the first dose of study treatment will be considered. The proportion of patients in the DDR Deficient Measurable Disease population with confirmed PSA decline ≥50% compared to baseline will be calculated along with the 95% CI using the Clopper-Pearson method (Clopper-Pearson; 1934).

9.3.2.4. CTC Count Conversion Rate

The CTC count conversion rate will be defined as the proportion of patients with a CTC count ≥5 CTC per 7.5 mL of blood at study entry that decreases to <5 CTC per 7.5 mL of blood anytime on study. CTC counts <5 CTC per 7.5 mL of blood will be considered favorable and CTC counts ≥5 CTC per 7.5 mL of blood will be considered unfavorable. The conversion rate will be calculated along with the 95% CI using the Clopper-Pearson method (Clopper-Pearson; 1934). Patients with a CTC count <5 per 7.5 mL of blood at baseline are not analyzed for this conversion endpoint, though they are included in continuous summaries. In addition, the proportion of patients with a CTC count of 1 or more (detectable) per 7.5 mL of blood at study entry that decreased to CTC=0 (undetectable) per 7.5 mL of blood any time on study will be assessed. The conversion rate will be calculated along with the 95% CI using the Clopper-Pearson method (Clopper-Pearson; 1934). Patients with a CTC count of 0 per 7.5 mL of blood at baseline are not analyzed for this conversion endpoint, though they are included in continuous summaries. The proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline will also be assessed.

9.3.2.5. Time to PSA Progression

The time to PSA progression is defined as the time from first dose of talazoparib to the date that a ≥25% increase in PSA with an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline) is documented, confirmed by a second consecutive PSA value obtained ≥3 weeks (21 days) later. Kaplan-Meier estimates will be presented together with a summary of associated statistics including the median and quartiles with two-sided 95% CIs. Conventions for censoring will be presented in the statistical analysis plan.

9.3.2.6. Radiographic PFS

Radiographic PFS is defined as the time from first dose of talazoparib to radiographic progression in soft tissue per RECIST 1.1 by independent central review, in bone per PCWG3 by independent central review, or death due to any cause, whichever occurs first. Details on the conventions for censoring PFS will be presented in the statistical analysis plan. Radiographic PFS will be estimated using the Kaplan-Meier method; the 95% CI for median time will be calculated using the Brookmeyer-Crowley method (Brookmeyer & Crowley, 1982). Analyses based on assessment by the investigator will also be performed.

9.3.2.7. Overall Survival

Overall survival is defined as the time from first dose of talazoparib to death due to any cause. Details on the conventions for censoring will be presented in the statistical analysis plan. Kaplan-Meier methods will be used to estimate overall survival. The 95% CI for median overall survival time will be calculated using the Brookmeyer-Crowley method (Brookmeyer & Crowley, 1982).

9.3.2.8. Patient Reported Pain

Pain assessed by the BPI-SF will be summarized using descriptive statistics by study visit.

Patient-reported outcomes assessments will be analyzed using the PRO population. Missing items will be handled per the scoring manuals of each questionnaire administered.

Deterioration in pain is defined as ≥2-point increase from baseline using question 3 of the BPI-SF. Additional pain and analgesic assessments will be completed for 7 consecutive days before study visits. Four or more completed daily pain reports at each reporting time period are required for a patient to be considered evaluable. Pain score averages during each reporting period will be calculated.

In order to adequately measure pain, it is equally important to adequately track analgesic use to ensure that the pain palliation observed is not the result of an increase in analgesic use but rather the effect of the antitumor treatment being studied. Analgesic data (from the analgesic log) will be mapped to the WHO analgesic usage score and used concurrently to define pain progression with the BPI SF (Basch E et al, 2013).

Time to deterioration in pain will be summarized using the Kaplan-Meier method and will include the median and 95% CIs based on the Brookmeyer-Crowley method. Longitudinal mixed effects model analyses will be used to assess change from baseline in pain symptoms.

9.3.2.9. Patient-Reported General Health Status (and Health Index)

A patient-reported general health status assessed by the EQ-5D-5L will be summarized using descriptive statistics. Longitudinal mixed effects model analyses will be used to assess change from baseline in general health status. In addition, there will be a health status profile analysis consisting of a display of the number and percentage of patients in each of the 5 response levels for each of the 5 dimensions at each visit.

9.4. Safety Analyses

All safety analyses will be performed using the safety population, defined as all patients who receive any amount of any study drug. Drug exposure will be summarized using descriptive statistics. Treatment-emergent safety data will be collected from the first dose of study treatment through 28 days after the last dose (ie, permanent discontinuation) of study drug or before initiation of new antineoplastic or investigational therapy, whichever occurs first. The safety of talazoparib will be evaluated by the analysis of incidence of serious and nonserious adverse events, severity of adverse events, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs. 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 4.03. The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Descriptive statistics will be used. Laboratory values will be classified by severity using the CTCAE, version 4.03. Laboratory shift tables of baseline to maximum postbaseline results to each subsequent visit will be produced as appropriate.

9.5. Pharmacokinetic Analyses

PK data analyses will include descriptive summary statistics of the predose and postdose plasma concentrations of talazoparib by study visit. In addition, the PK data from this study may be used to develop a population PK model. CCI [redacted]

CCI [redacted]

[redacted]

9.7. Determination of Sample Size

At least 100 patients will be enrolled with soft tissue measurable disease (per RECIST1.1) and alterations in DNA damage repair genes, determined at prescreening (optional) or screening by the gene mutation biomarker panels used for the assessment of tumor tissue DNA.

- Patients with DNA damage repair deficiencies assessed using the gene mutation biomarker panels used for the assessment of a panel of genes likely to sensitize to PARP inhibition (N = 100).

With 100 patients the ORR can be estimated with a maximum standard error of 5.1%. A sample size of 100 patients is sufficient to demonstrate that if the observed best ORR is ≥23%, the lower bound of the corresponding exact 2-sided 95% CI excludes 15.2%. Table 14 provides the response rates and exact 95% CI for 100 patients based on different scenarios.

Table 14. Response Rates and Exact 95% CI for 100 Patients

Number of Responders	ORR point Estimate	Lower 95% CI of ORR	Upper 95% CI of ORR
23	23%	15.2%	32.5%
33	33%	23.9%	43.1%
43	43%	33.1%	53.3%
50	50%	39.8%	60.2%

9.8. Interim Analysis

The study is designed to have an initial analysis for safety and efficacy and an interim analysis for efficacy. The initial analysis will be performed after 20 patients from the DDR deficient measurable disease population receive study treatment for at least 8 weeks. The subsequent interim analysis will be performed when 60 patients form the DDR deficient measurable disease population complete at least 6 months of study treatment or are otherwise no longer being followed (ie, have, withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up).

An interim analysis with at least 60 patients is planned and if the observed best ORR is ≥23%, the lower bound of the corresponding exact 2-sided 95% CI would exclude <13%.

With 60 patients, the ORR can be estimated with a maximum standard error of 6.6%. Table 15 provides the exact binomial 95% CI for ORR for 60 patients based on different observed responses.

Table 15. Response Rates and Exact 95% CI for 60 Patients

Number of Responders	ORR point Estimate	Lower 95% CI of ORR	Upper 95% CI of ORR
14	23.3%	13.4%	36%
20	33.3%	21.7%	46.7%
26	43.3%	30.6%	56.8%
30	50%	36.8%	63.2%

As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

9.9. Data Monitoring Committee

This study will not use a Data Monitoring Committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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 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 patient chart. In these cases, data collected on the CRFs must match the data in 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.

11.2. Data Protection

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

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff has 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, participants will be assigned a single, participant specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

11.3. 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, and 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.

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 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.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study patients. 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 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 patients fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative or legal guardian, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

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.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all [other] participating countries is defined as last patient last visit (LPLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of talazoparib at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) as quickly as is practical. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com.

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

16. REFERENCES

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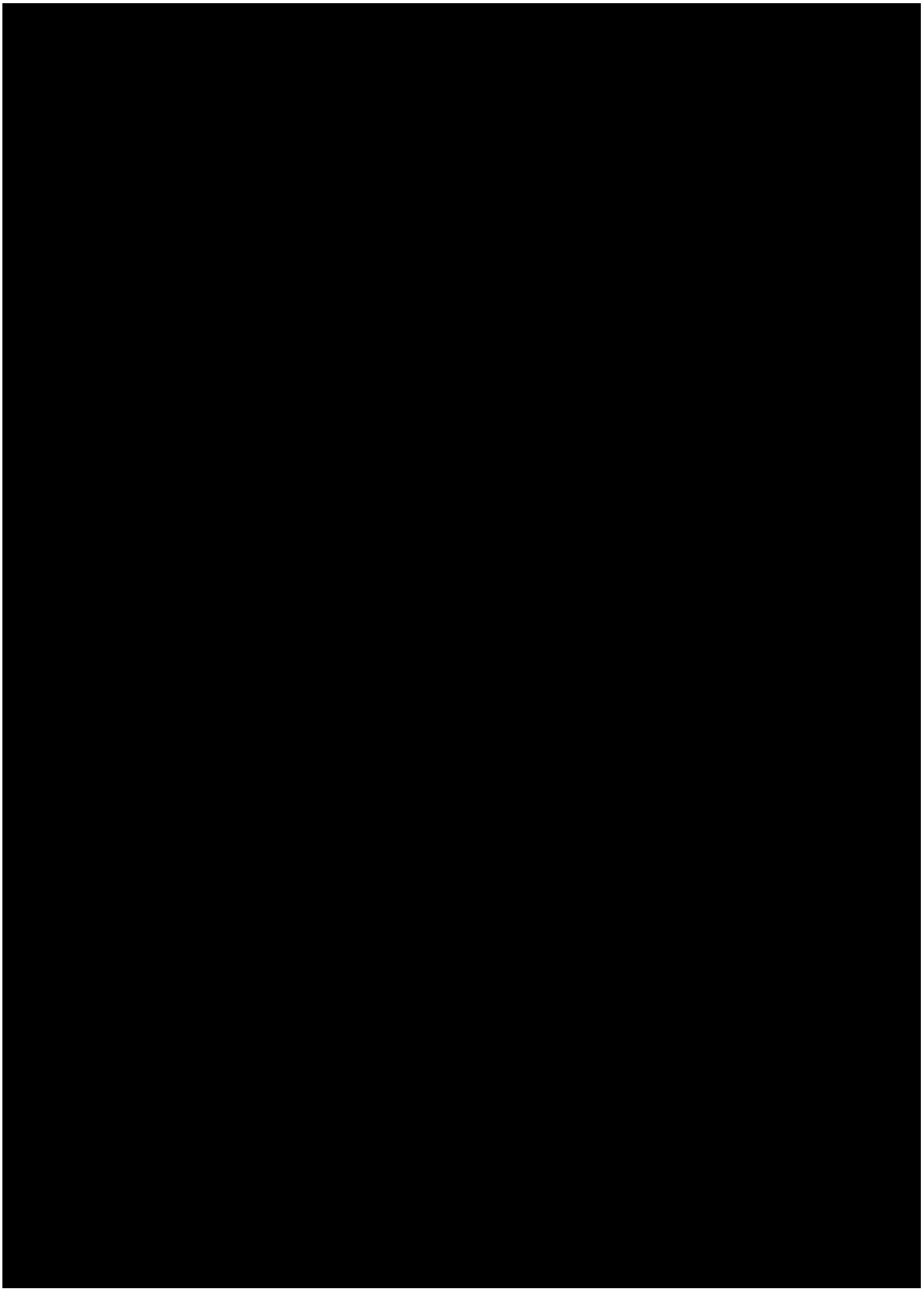
Appendix 1. Abbreviations

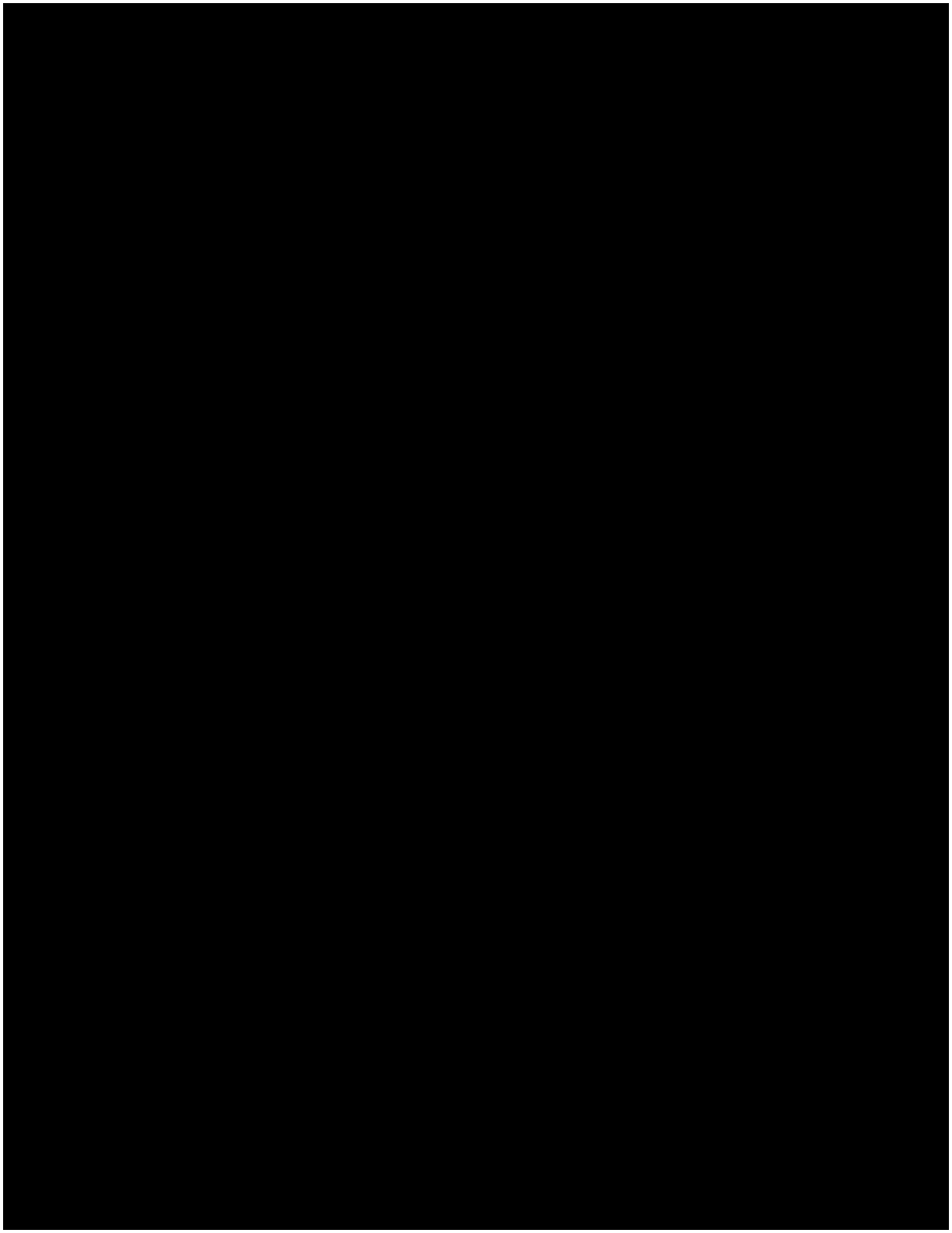
The following is a list of abbreviations that may be used in the protocol.

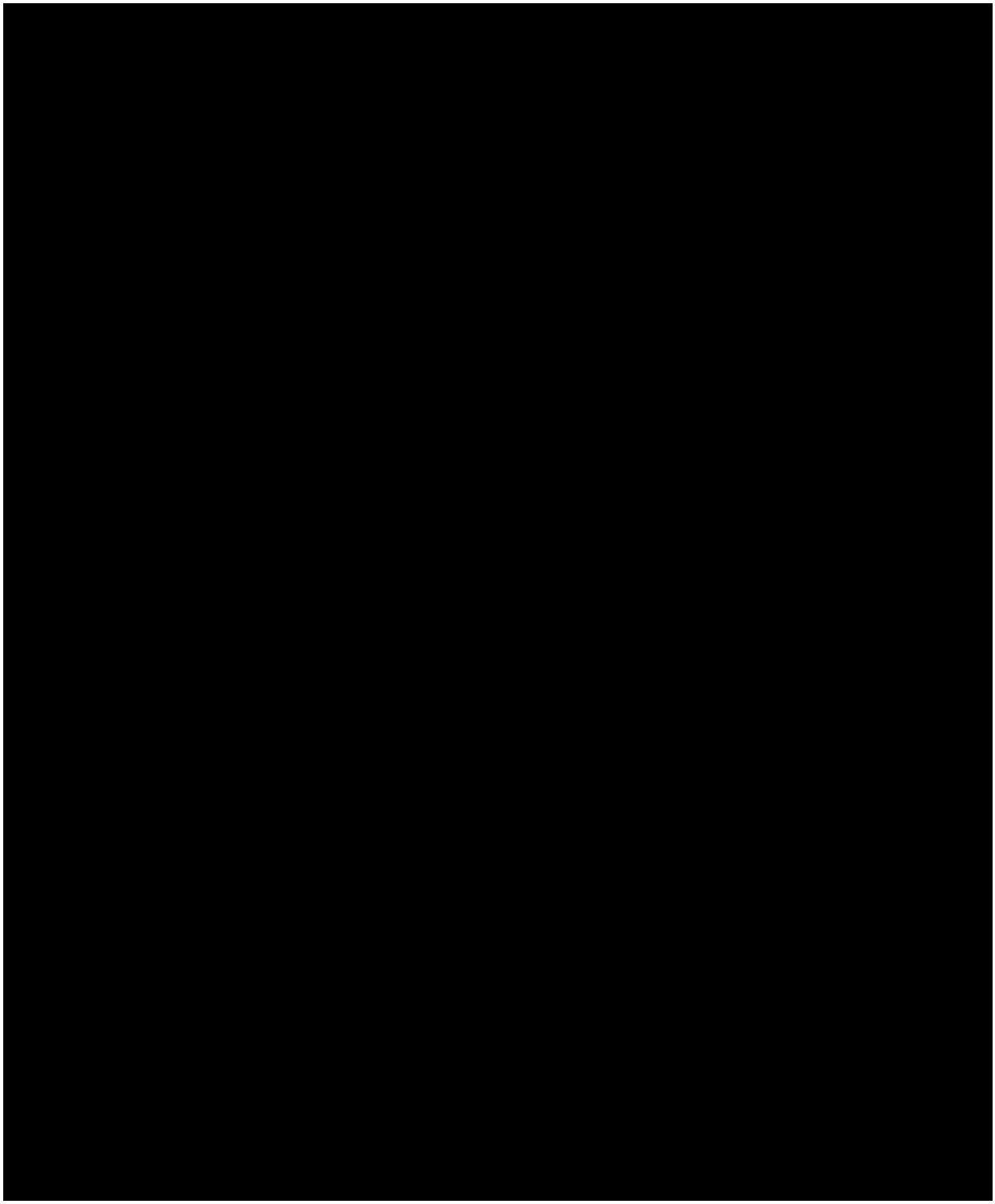
Abbreviation	Term
ADP	adenosine disphosphate
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time zero to the time 24 hours (dosing interval).
BALB/c	Bagg Albino inbred research mouse strain c
CCI	[redacted]
BCRP	breast cancer resistant protein
BMN	BioMarin
BPI-SF	Brief Pain Inventory-Short Form
C_{max}	maximum plasma concentration
C_{min}	mean plasma trough concentration
CI	confidence interval
CK	creatine kinase
CL/F	apparent oral clearance
COMET	Carvedilol Or Metoprolol European Trial
COX-2	cyclooxygenase-2
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRPC	castration-resistant prostate cancer
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CCI	[redacted]
CT	computed tomography/clinical trial
CTA	clinical trial application
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CT SAE	Clinical trial serious adverse event
CYP	cytochrome 450
DDR	deoxyribonucleic acid damage repair
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
E-DMC	External Data Monitoring Committee
eGFR	estimated glomerular filtration rate
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EORTC	European Organisation for Research and Treatment of Cancer

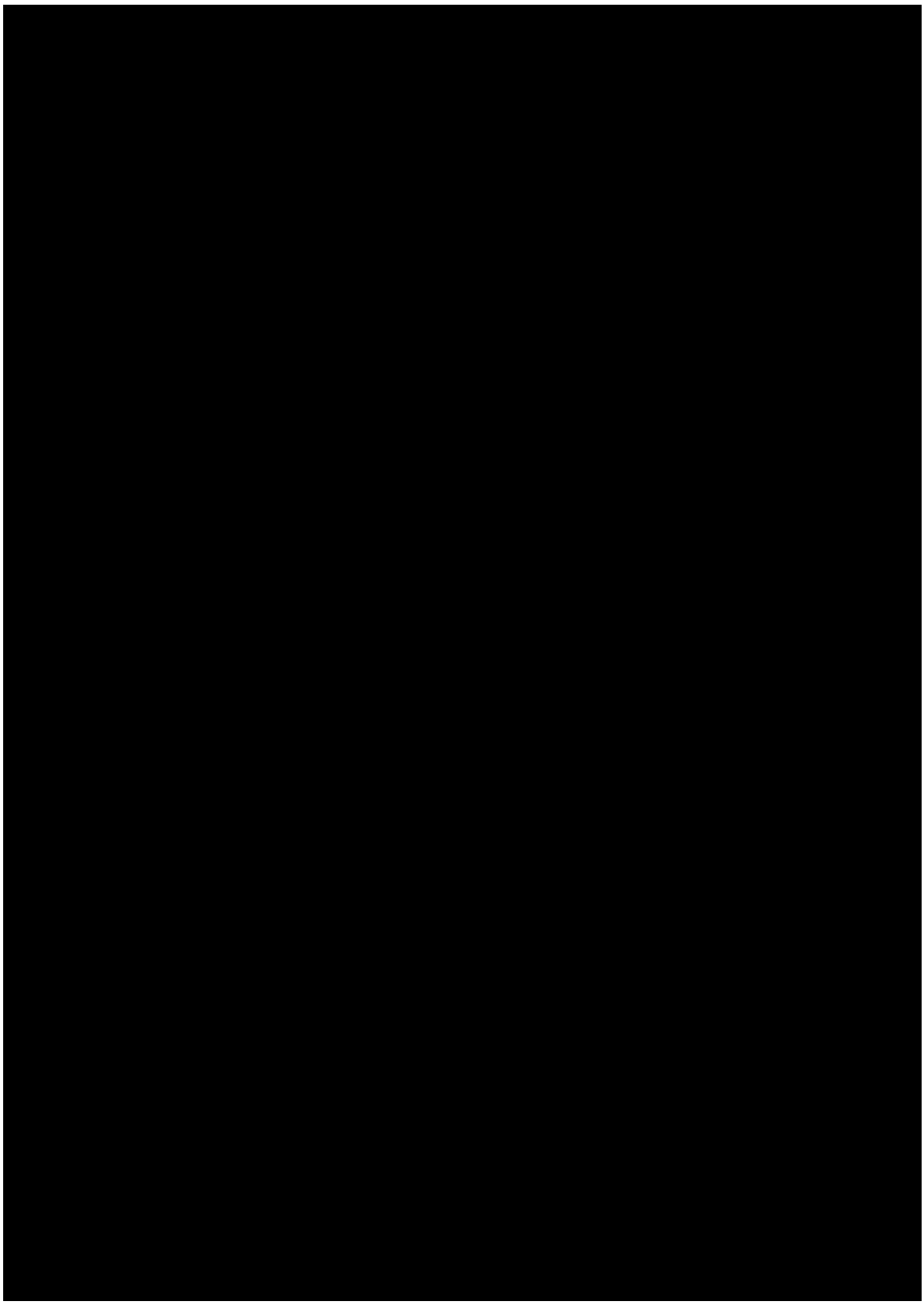
Abbreviation	Term
EQ-5D-5L	European Quality of Life 5-Dimension, 5-Level Scale
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GnRH	gonadotropin-releasing hormone
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNPC	hormone-naïve prostate cancer
HR	hazard ratio
HRD	homologous recombination deficiency
HRQL	health-related quality of life
IC50	half -maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICD	informed consent document
ICR	independent central review
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
Ki	inhibitory constant
LFT	liver function test
LPLV	last patient last visit
M0	nonmetastatic
M1	metastatic
mCRPC	Metastatic castration-resistant prostate cancer
MDRD	Modification of Diet in Renal Disease
MDS	myelodysplastic syndrome
MDV	Medivation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NAD	nicotinamide adenine dinucleotide
NASH	Nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next generation sequencing
NHT	novel hormonal therapy
NLCB	no longer clinically benefitting

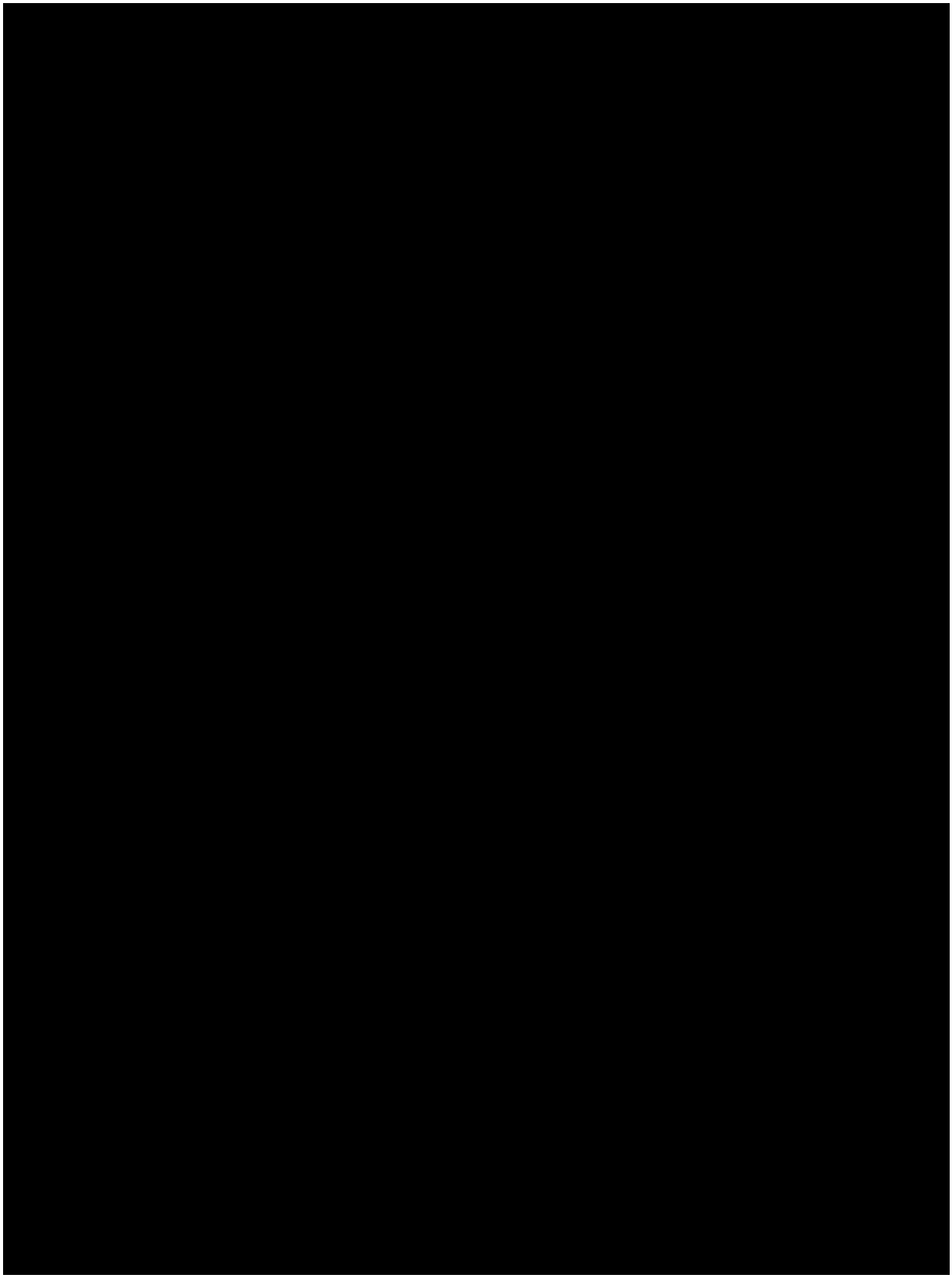
Abbreviation	Term
NSAIDS	Nonsteroidal anti-inflammatory drugs
ORR	Objective response rate
P-gp	P-glycoprotein
PARP	poly(adenosine diphosphate-ribose) polymerase
PCD	primary completion date
PCT	Physician's choice chemotherapy
PCWG	Prostate Cancer Working Group
PD	pharmacodynamics(s)
PF	Pfizer
PFS	progression-free survival
PGx	pharmacogenomics(s)
PI	principal investigator
PID	patient identification
PK	pharmacokinetic
PR	partial response
PR-25	Quality of Life Questionnaire Prostate Cancer Module
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	prothrombin time
QoL	quality of life
QLQ-C30	Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCLC	Small cell lung cancer
SMQ	Standardized MedDRA Query
SOP	standard operating procedure
SRSD	single reference safety document
SSID	single subject identification
SUSAR	suspected unexpected serious adverse reaction
SPARC	Satraplatin and Prednisone Against Refractory Prostate Cancer;
TALAPRO	TALAzoparib PROstate
TBili	total bilirubin
TEAE	treatment-emergent adverse event
Tmax	Time to mean maximum plasma concentration
TOPARP-A	Trial of Olaparib in Patients With Advanced Castration Resistant Prostate Cancer, part A
ULN	upper limit of normal
US	United States
V/F	volume of distribution
WHO	World Health Organization

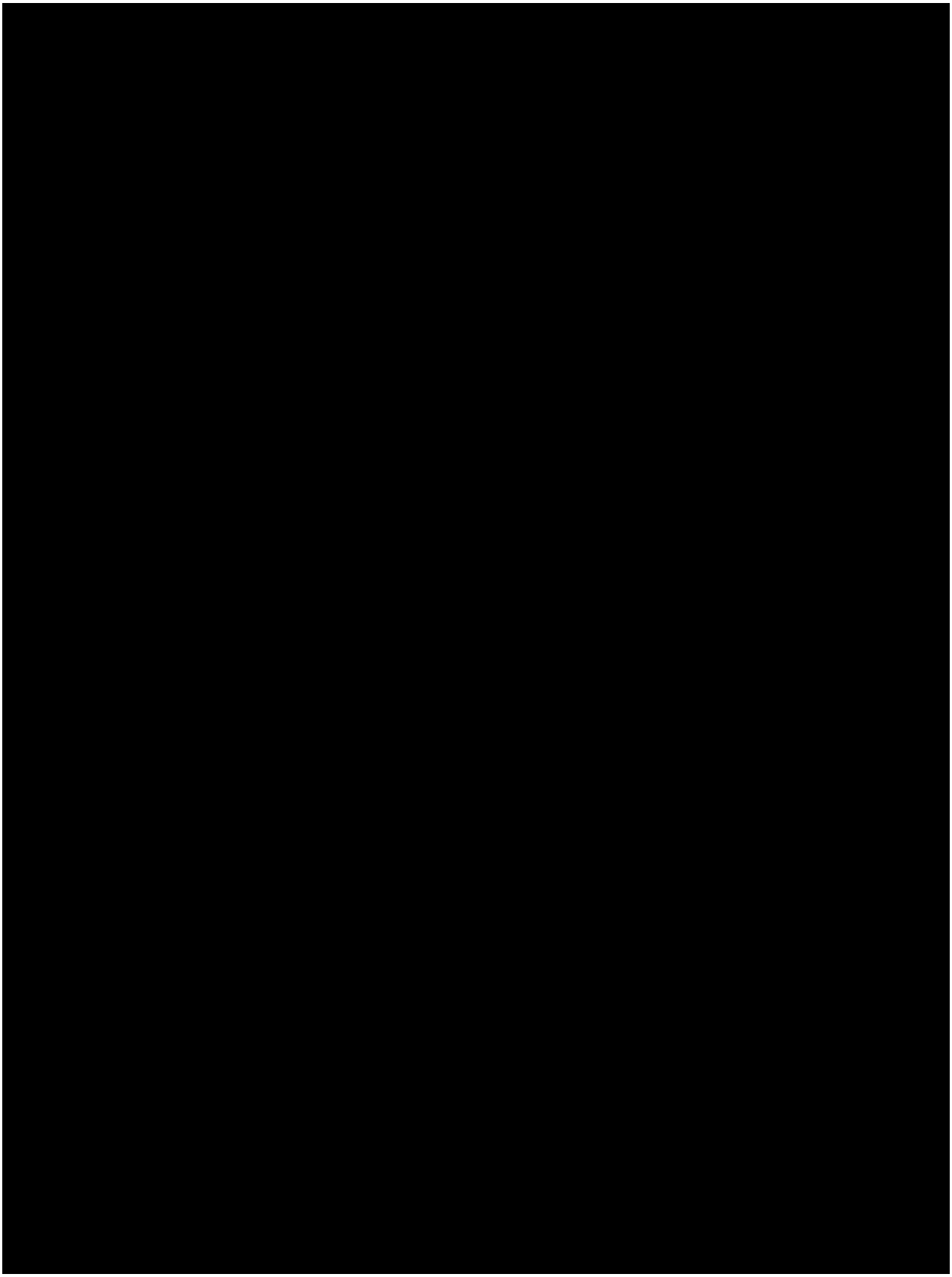


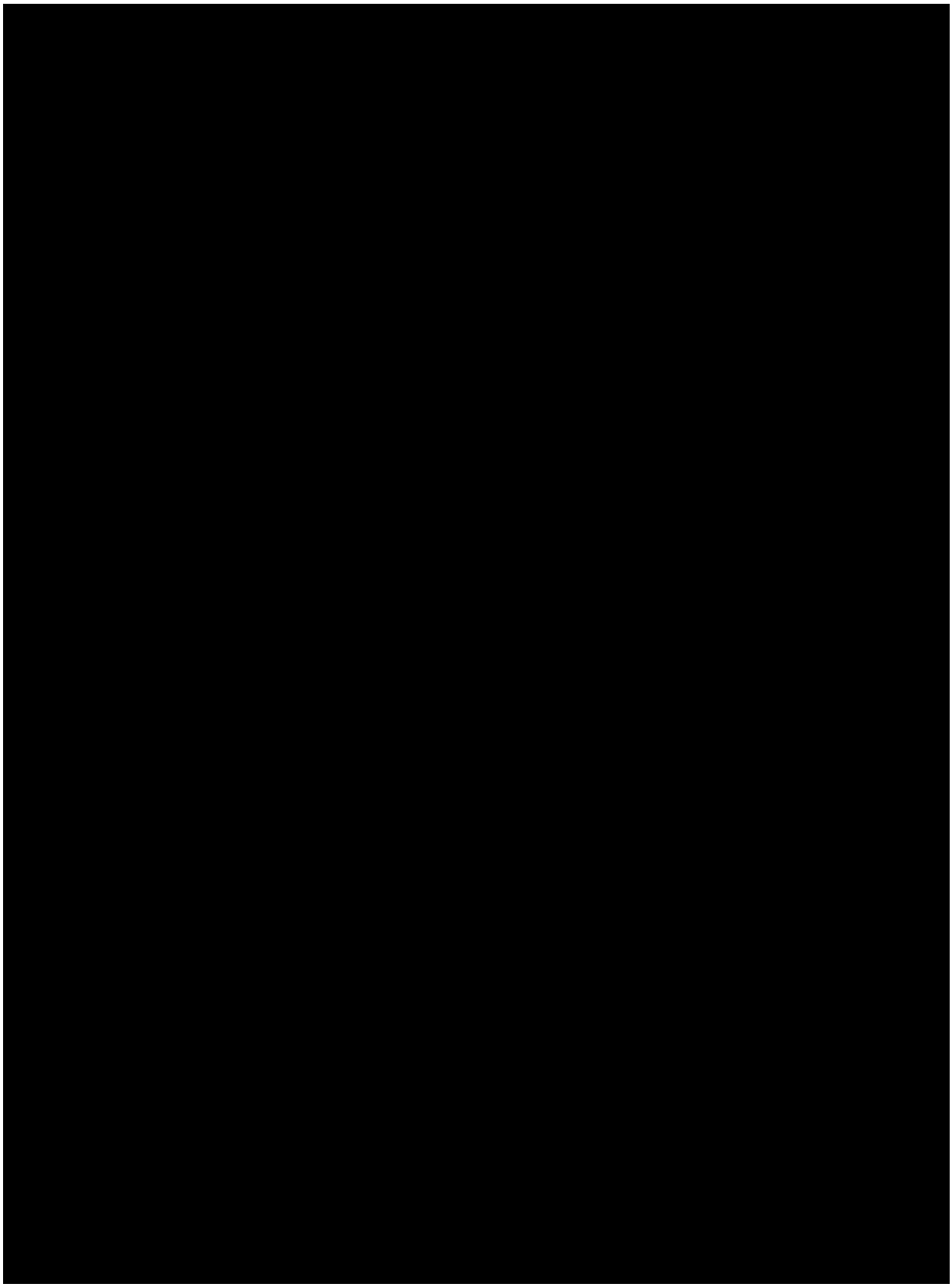


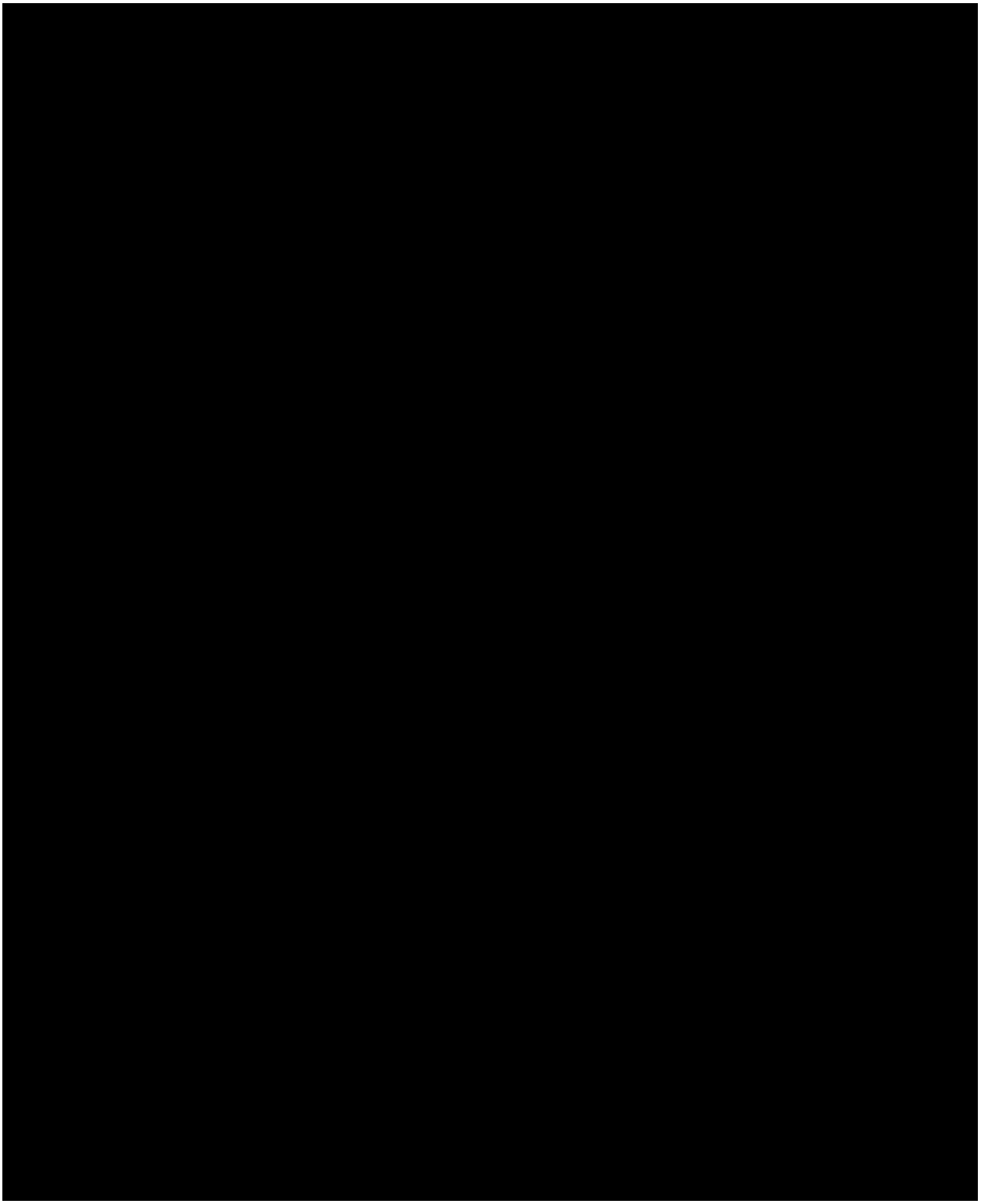


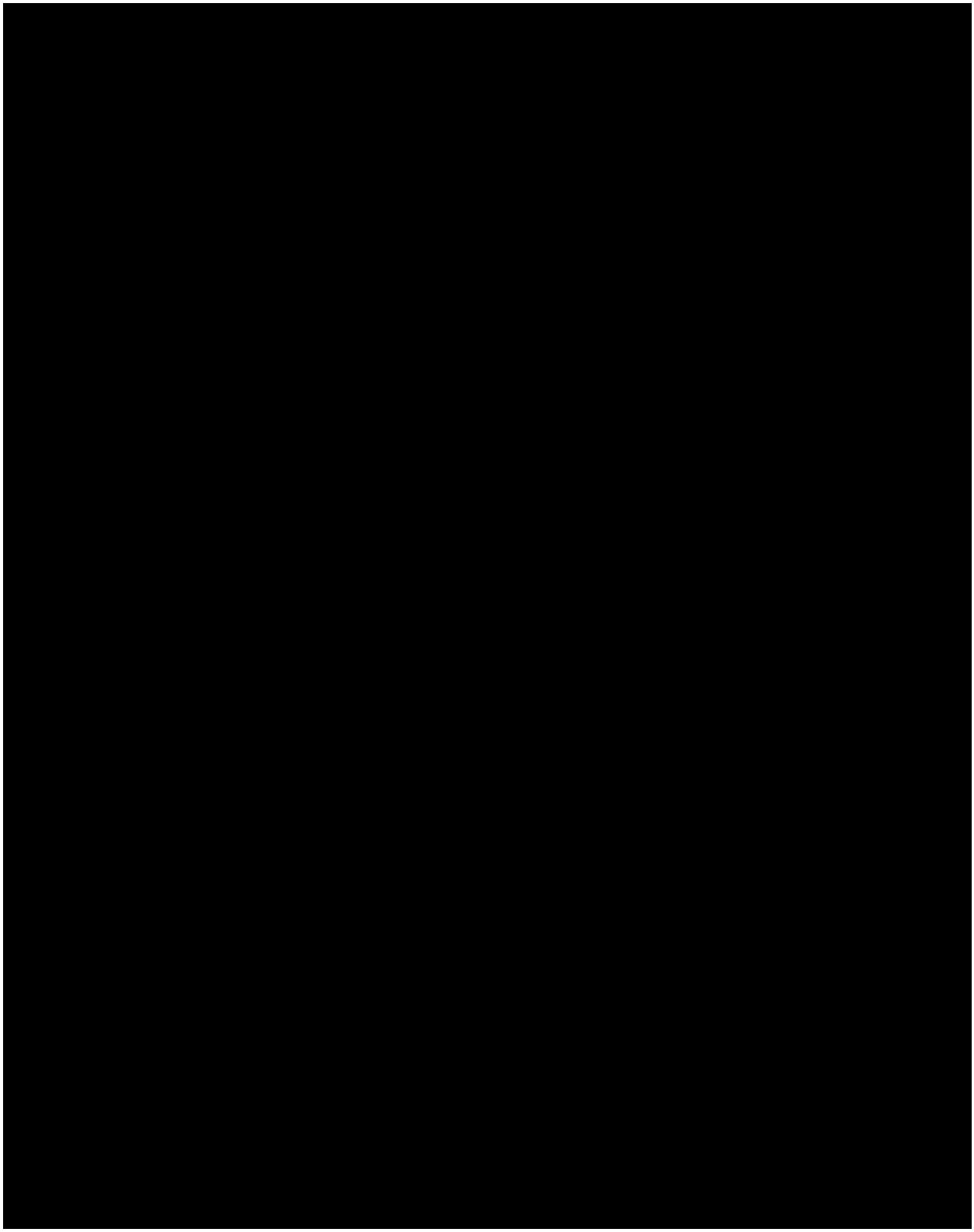


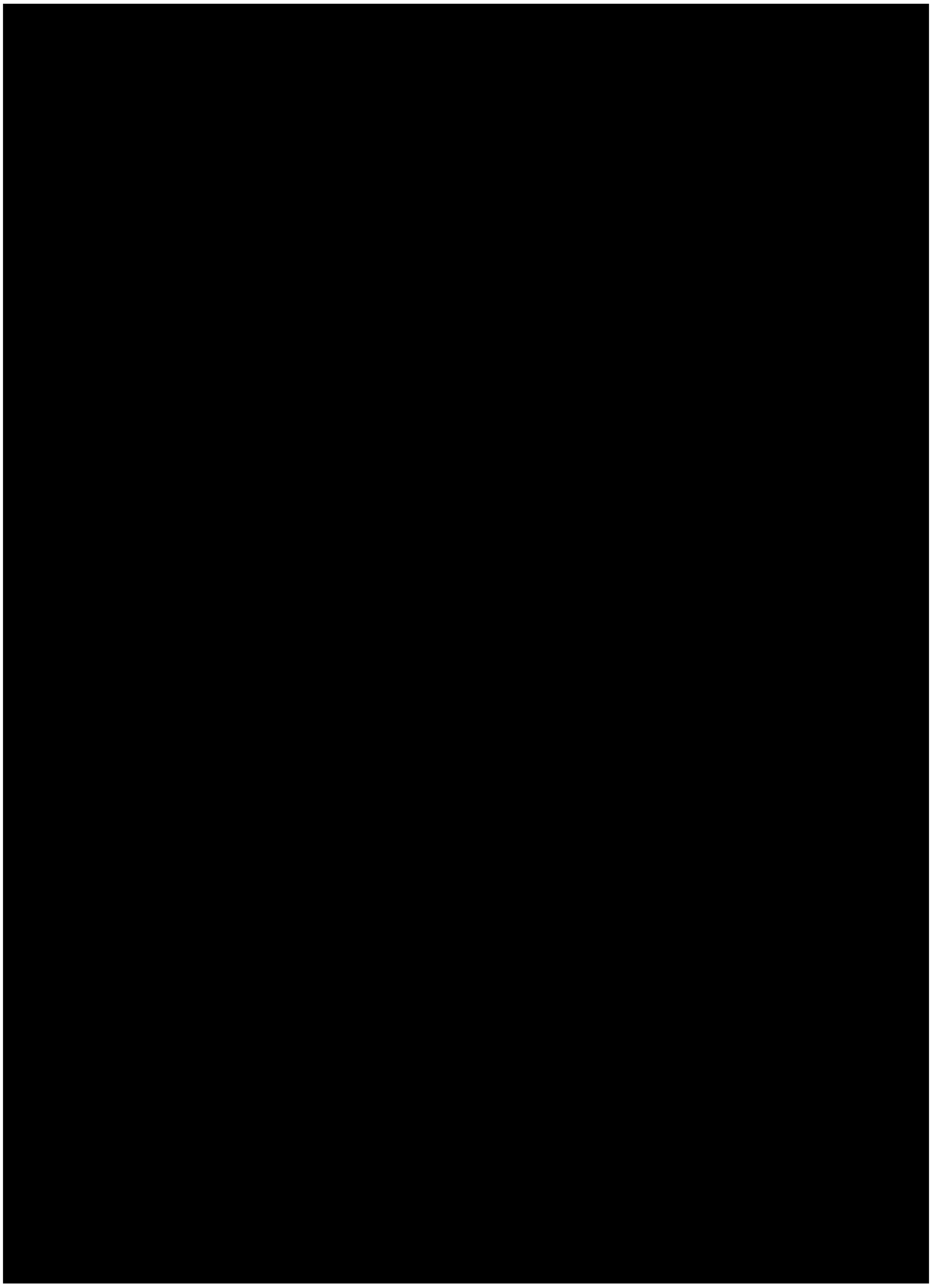












Appendix 6. Country-Specific Amendment: France

This appendix applies to study sites located in France.

Institutional Review Board/Ethics Committee

Ethic Committee and health authority approval will be obtained for any substantial protocol amendments and informed consent revisions before implementing the changes.

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.

Investigational Product

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

Appendix 7. Country-Specific Documentation: Germany

This appendix applies to study sites located in Germany.

Per German law, it is prohibited to enroll in clinical studies any persons who have been housed in an institution following a regulatory or judicial order. Consistent with the inclusion criterion 18 of the TALAPRO-1 protocol amendment 4 ("Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures") and in accordance with German law, institutionalized patients will not be able to participate in the TALAPRO-1 study.