# Title Page

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| Protocol Title: | A Phase 1b/2a Multicenter Study of NOX66 and External Beam Radiotherapy in Patients with Metastatic Castration-resistant Prostate Cancer and Other Solid Tumors |
| Compound: | NOX66 (active ingredient: Idronoxil) |
| Trade Name: | Not applicable |
| Indication: | Metastatic castration-resistant prostate cancer and other solid tumors |
| Study Sponsor: | Noxopharm Limited<br>PO Box 292<br>Gordon, NSW 2072<br>Australia |
| Sponsor Protocol Number: | NOX66-005 |
| Development Phase: | Phase 1b/Phase 2a |
| Regulatory Agency Identifying Number: | 154874 |
| Approval Date: | Final 3.0, 21 Jan 2022 |

**Sponsor Signatory:**

| | |
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| Dr Gisela Mautner<br>Chief Medical Officer | Date |

**Medical Monitor Name and Contact Information** will be provided separately.

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# 1 Protocol Summary

## 1.1 Synopsis

**Protocol Title:** A Phase 1b/2a Multicenter Study of NOX66 and External Beam Radiotherapy in Patients with Metastatic Castration-resistant Prostate Cancer and Other Solid Tumors

**Sponsor Protocol No.:** NOX66-005

**Development Phase:** Phase 1b/Phase 2a

**Sponsor:** Noxopharm Limited

**Study Sites and Locations:** Approximately 14 sites in Australia, United States and Europe

**Rationale:**

Idronoxil, which is the active ingredient of the NOX66 formulation, is a synthetic flavonoid derivative of genistein that inhibits external Ecto-NOX disulfide-thiol exchanger (ENOX) 2 to induce apoptosis. ENOX2 inhibition activates the sphingomyelinase pathway and deactivates the antiapoptotic protein kinase B pathway, a key driver of radiotherapy resistance. The targeted effect on ENOX2 has the potential to limit toxicity to non-cancer cells, which preferentially express ENOX1. Previous studies have demonstrated improved radiation sensitivity in prostate cancer with flavonoid derivatives. Early studies of intravenous and oral formulations of idronoxil were hampered by limited bioavailability. The Sponsor has sought to address the problem of extensive drug metabolism through the development of a rectal suppository dosage form. With blood draining from the distal part of the rectum directly into the inferior vena cava, first pass liver metabolism can be avoided. In the case of a diphenolic drug such as idronoxil, the bioavailability is augmented by the rectal mucosa being known to be devoid of transferase activity and therefore the phase II metabolism is significantly reduced. These two aspects combined are the basis for the rationale that idronoxil delivered via the rectum is subjected to less phase I and phase II metabolism than that observed for orally administered idronoxil. NOX66 is a suppository dosage form of idronoxil in a proprietary fatty base containing a surfactant. This formulation is novel in that a lipophilic active ingredient is dispersed in a lipophilic suppository base – compared with traditional suppository formulations whereby a hydrophilic base would normally be utilized. Moreover, this suppository dosage form provides a slow and sustained release of idronoxil comparable to an intravenous infusion.

The first clinical study with NOX66 (NOX66-001A) was a Phase 1a/1b study in which NOX66 was evaluated both as a monotherapy and in combination with carboplatin, in patients with refractory solid tumors. Two breast cancer (BC) patients and one ovarian cancer patient enrolled in this study had reductions in target lesions size with one BC patient showing target lesion disappearance (as per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1.) at the end of the study.

The NOX66-002A study evaluated NOX66 in combination with external beam radiotherapy (EBRT) in patients with metastatic castration-resistant prostate cancer (mCRPC). Twenty-five patients received radiation therapy and 7 to 16 days of NOX66 treatment in this study.

The overall radiological assessment according to RECIST v1.1 at 3 months for 19 evaluable patients resulted in 17 patients with disease control (1 patient in the 800 mg and 2 patients in 1200 mg dose cohort with partial response [PR], 14 patients with stable disease [SD]) and 2 patients, 1 each in the 400 mg and 800 mg cohorts, respectively, with disease progression. At 6 months and of the 15 evaluable patients, 1 continued to have PR and 60% continued to have SD. There were two changes among the patients with PR in the 1200 mg cohort, with 1 patient not evaluable due to withdrawal and the other patient progressing to disease progression by RECIST v1.1 criteria while maintaining a prostate-specific antigen (PSA; 69%) and pain response (69% in overall pain score).

The overall disease control rate (DCR) at 6 months was 66.6% (10/15), with 9 patients having SD and 1 patient PR. The patient with PR also had a PSA decrease of 86% and a symptom control response of being 100% pain-free. A clinical meaningful response in a non-irradiated lesion was also observed in the same patient, with a reduction in tumor size of 26.1% from baseline at 3 months and a continued decline to 49.3% at 6 months (abscopal response). Four of 15 patients had an abscopal response in non-irradiated lesions that were outside of the radiation field.

NOX66 is designed to improve drug delivery and exposure of idronoxil to tumor cells. This Phase 1b/Phase 2a clinical study will explore higher doses of NOX66 and expand the experience of NOX66 in men with mCRPC and patients with other solid tumors to determine the recommended Phase 2 dose (RP2D) and provide preliminary evidence on overall tumor response rate, survival, symptomatic relief of pain as well as other symptoms of this disease, and effects on PSA levels (for mCRPC patients only).

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary Objectives and Endpoints** | |
| Part 1 (Dose Escalation):<br><br>To determine the MTD and RP2D of NOX66 in combination with low-dose EBRT in patients with any solid tumor | The primary objective for Part 1 will be determined based on the count of DLTs.<br>• MTD is defined as the dose level at which no more than 1 patient out of 6 experiences a DLT at the end of Cycle 1.<br>• RP2D is the highest dose administered at which no more than 1 patient out of 6 experiences a DLT at the end of Cycle 1 and the dosage form, including the dosing frequency, is acceptable to patients. |
| Part 2 (Dose Expansion):<br>Arm 1: To evaluate the effect of NOX66 on PSA response in patients with mCRPC.<br><br>Arm 2: To evaluate the effect of NOX66 on DCR in patients with BC and NSCLC. | • PSA response is defined as the proportion of patients with a reduction in PSA in plasma (ng/mL) of ≥ 30% from baseline at the end of Cycles 3 and 6.<br>• DCR is measured by the percentage of patients with a best overall confirmed response of CR or PR and SD. |
| **Secondary Objectives and Endpoints** | |
| Characterize the safety and tolerability of NOX66 | Safety and tolerability of NOX66 as determined by AEs, TEAEs, clinical laboratory evaluations, vital signs, 12-lead ECG and physical examinations. |
| Evaluate the safety and tolerability of both doses of EBRT | Safety and tolerability of both doses of EBRT as determined by AEs, TEAEs, clinical laboratory evaluations, vital signs, 12-lead ECG and physical examinations. |
| Evaluate the exposure of idronoxil | Concentration of idronoxil and selected metabolites in plasma and derived PK parameters, including but not limited to: $C_{max}$, $T_{max}$, $AUC_{(0-t)}$, $AUC_{(0-6)}$, $AUC_{(0-12)}$, $AUC_{(0-inf)}$, $C_{min}$ and $t_{½}$, as data permit. |

| Objectives | Endpoints |
|---|---|
| Evaluate the preliminary clinical efficacy of NOX66 plus low-dose EBRT in patients with mCRPC and other solid tumors | Preliminary clinical efficacy as determined by:<br>• Change from baseline in PSA (mCRPC only) at any time point.<br>• Overall response rate assessed by RECIST v1.1 criteria (all tumor types) and PCWG-3 criteria (mCRPC).<br>• Duration of response (for patients with measurable disease).<br>• Change from baseline ECOG scores.<br>• Change from baseline in tumor size and number.<br>• PFS and OS. |
| Explore the effects of NOX66 on pain and other cancer-related signs and symptoms | Effects on pain and other cancer-related signs and symptoms as determined by:<br>• Change from baseline in pain scores based on the BPI-SF questionnaire.<br>• SREs and SSEs.<br>• Change of dose and frequency of morphine administration and analgesic use. |
| Evaluate the QoL using PRO questionnaires | QoL as assessed by:<br>• Change from baseline in PEQ.<br>• Change from baseline in EORTC-QLQ-C30.<br>• Change from baseline in FACT-P (mCRPC only). |
| **Exploratory Objectives and Endpoints** | |
| Characterize the relationship between pharmacodynamic biomarkers and idronoxil plasma concentrations (if a meaningful change is observed) | • Change in biomarkers (cytokines, chemokines and ctDNA) from baseline.<br>• Change in lipid profile from baseline. |

AE = adverse event; BC = breast cancer; BPI-SF = Brief Pain Inventory – Short Form; CR = complete response; ctDNA = circulatory tumor deoxyribonucleic acid; DCR = disease control rate; DLT = dose-limiting toxicity; EBRT = external beam radiotherapy; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients; FACT-P: Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; MTD = maximum tolerated dose; NSCLC = non-small-cell lung cancer; OS = overall survival; PCWG-3 = Prostate Cancer Working Group 3; PEQ = Patient Experience Questionnaire; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; PRO = Patient Reported Outcome; PSA = prostate-specific antigen; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SD = stable disease; SRE = skeletal-related events; SSE = symptomatic skeletal events; TEAE = treatment-emergent adverse event

**Overall Design:**

This is a Phase 1b/Phase 2a, open-label, multicenter study to determine the safety, tolerability, RP2D, efficacy, pharmacokinetics (PK) and pharmacodynamic (PD) properties of idronoxil when rectally administered as a suppository (NOX66) to patients with any solid tumor (Part 1) and patients with mCRPC, BC and non-small-cell lung cancer (NSCLC) (Part 2) who are eligible for low-dose EBRT for at least one symptomatic or minimally symptomatic lesion (for the prevention of symptoms). The study is divided into 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion). The study design allows an exploration of different doses of NOX66 (800 mg, 1200 mg, 1600 mg and 2400 mg) with safety monitoring to ensure the safety of the patients. A Safety Steering Committee (SSC) will review available safety data after the first cycle (21 days) of each dose cohort of NOX66 in Part 1 to determine the maximum tolerated dose (MTD)/RP2D.

In Cycle 1, NOX66 will be administered for 14 days followed by a 7-day rest period on a 21-day cycle. From Cycle 2 onwards, NOX66 will be administered for 7 days followed by a 7-day rest period on a 14-day cycle. Patients will continue to receive NOX66 on a cyclical basis until disease progression, unacceptable toxicity, withdrawal of consent, start of a new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by the Sponsor.

The study population consist of patients with mCRPC, BC, NSCLC or other solid tumors who have failed at least one line of prior treatment and for whom, according to the Investigator, are eligible for low-dose EBRT for at least one symptomatic or minimally symptomatic lesion (for the prevention of symptoms).

The dose levels of EBRT will be either:

- 8 Gray (Gy) as a single fraction, or
- 20/25 Gy as 5 fractions given over 5 to 10 days.

The first EBRT dose fraction must be administered on Day 2 of Cycle 1 and the remaining dose fractions will be given between Day 3 and Day 11. The choice of one of the EBRT dose/fractions stated above will be at the discretion of the Investigator and will be determined by the clinical requirements of the patient. EBRT will be administered according to the institutional protocol.

The expected study duration for each patient from initial administration of NOX66 until the last study visit is determined by the number of treatment cycles each patient receives plus the follow-up period, which is from the last dose of NOX66 until death or the patient is lost to follow-up.

The study will finish when the last patient enrolled in Part 2 completes 6 months of treatment and all patients receiving study drug at that time will be switched to the NOX66 compassionate access program. Those patients on the compassionate access program will continue to receive NOX66 treatment until disease progression or unacceptable toxicity. These patients will be followed until death, or the patient is lost to follow-up.

There will be a Screening period of up to 27 days (Days -28 to -2). Each patient will attend the study center on Day -1 of Cycle 1 for eligibility assessments and on all PK days (Cycle 1: Days 1, 2, 6, 14 and 15; Cycles 2 and 3: Days 1 and 8). Patients in Part 1 may require an overnight stay on Day 1 of Cycle 1. On Days 1, 2, 6 and 14 of Cycle 1 and Day 1 of Cycles 2 and 3, the NOX66 morning administration will occur at the study center under medical supervision. During these days blood samples for PK analysis will be collected as per the schedule mentioned in Table 1-3. In addition to PK samples, patients will be monitored for cardiac effects using 12-lead electrocardiograms (ECGs) (Table 1-2). NOX66 will be self-administered by the patients or administered by their care giver at home on all other dosing days as well as the evening doses of NOX66 on PK days (Cycle 1: Days 2, 6 and 14; Cycles 2 and 3: Day 1). The evening dose of Day 1 of Cycle 1 (in Part 1 only) will be administered at the clinical unit. Patients or care givers should always wear gloves when handling and/or during administration of NOX66. The use of a small amount of water-soluble lubricant is advised before rectal administration. Further administration and handling instructions are provided in the "Instructions for Administration of NOX66 Suppositories" document. Patients will also attend the study center for EBRT (8 Gy or 20/25 Gy given as 1 or 5 fractionated doses, respectively) on Days 2 to 11 of Cycle 1 depending on the number of fractions administered. From Cycle 2 onwards only NOX66 will be administered for 7 days followed by a 7-day rest period (as indicated above). Patients with mCRPC may also receive androgen deprivation therapy as maintenance therapy and patients with BC may receive background hormonal therapy during this study. No other anticancer therapy will be allowed during the study. Patients will have an End of Treatment (EOT) Visit within 7 to 10 days after the last dose of study drug. If a patient discontinues the study early (Early Discontinuation [ED]), the patient will have an ED Visit within 7 to 10 days after the last dose of study drug.

Patients in both study parts will be followed up by phone for adverse events (AEs)/serious adverse events (SAEs) for 30 days after the last dose of study drug or until resolution or stabilization of ongoing AEs/SAEs deemed at least possibly related to the study drug, whichever is longer. All patients (including patients who discontinued the study early for reasons other than disease progression) will be followed up approximately every 12 weeks (± 2 weeks) after completion of the treatment period for disease progression up to 12 months, and for safety until death or the patient is lost to follow-up. Patients who discontinued the study early for reasons

other than disease progression will attend the clinical unit for the follow-up visits. Patients will receive the study drug until disease progression, unacceptable toxicity, withdrawal of consent, initiation of new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by the Sponsor. Patients who discontinued from the study for reasons other than progression will have tumor imaging and disease response assessments performed for up to 12 months after the last dose of study drug until disease progression, withdrawal of consent, initiation of new anticancer therapy, the patient is lost to follow-up or death, whichever comes first.

The study schemes are provided in Figure 1–1 (Part 1) and Figure 1–2 (Part 2), and the Schedule of Activities is provided in Table 1-1 (Parts 1 and 2).

**Part 1 (Dose Escalation)**

Approximately 30 patients with any solid tumor who require low-dose EBRT will be enrolled sequentially to the four planned NOX66 dose groups (Dose Cohort 1: 800 mg [3 to 6 patients]; Dose Cohort 2: 1200 mg; Dose Cohort 3: 1600 mg; Dose Cohort 4: 2400 mg [3 to 8 patients in each of Dose Cohorts 2 to 4]; total daily dose administered twice a day [BID]). At least 2 patients enrolled in Dose Cohorts 2 to 4 must have mCRPC.

The proposed dose regimen for Part 1 is given in the table below. No intra-subject dose escalation is allowed.

**Proposed Doses for NOX66 (Part 1)**

| | Dose Cohort | | | |
|---|---|---|---|---|
| | **1** | **2** | **3** | **4** |
| Total daily dose | 800 mg | 1200 mg | 1600 mg | 2400 mg |
| Dosing regimen | 400 mg BID | 600 mg BID | 800 mg BID | 1200 mg BID |
| Number of suppositories per day | 2 × 400 mg | 2 × 600 mg | 4 × 400 mg | 4 × 600 mg |

BID = twice daily

All patients will be closely monitored for any dose-limiting toxicities (DLTs) up to Day 21 of Cycle 1.

Dose escalation will be based on an adapted “3+3” design, where dose cohorts will be expanded for up to 6 patients (Dose Cohort 1) in the event of DLT or up to 8 patients (Dose Cohorts 2 to 4) to allow for robust estimation of PK parameters after being deemed “safe” based on the traditional “3+3” design.

At each dose level, 3 patients will initially be treated with NOX66.

- If none of the first 3 patients enrolled in Cohort 1 experience a DLT during the first treatment cycle, the dose will be escalated to the next level.
- If none of the first 3 patients experience a DLT during the first treatment cycle of Cohorts 2 to 4, then the dose level will be deemed "safe" and up to 5 additional patients will be enrolled to the current dose level for estimation of PK parameters. At the same time (with the exception of Cohort 4), the next dose level will be initiated and the first 3 patients will be enrolled to the escalated dose.
- If 1/3 patients experience a DLT, an additional 3 patients will be enrolled. If 1/6 patients experience a DLT then this dose level will be deemed "safe" and, for Cohorts 2 to 4, 2 more patients may be enrolled for estimation of PK parameters. At the same time, the next dose level will be initiated and the first 3 patients will be enrolled to the escalated dose.
- If > 1/3 or > 1/6 patients experience a DLT, then dose escalation will be halted, and the previous dose will be declared as the MTD.

If the 1200 mg dose is not tolerable (i.e., 2 or more patients with DLTs), an additional 3 patients will be enrolled in the 800 mg dose cohort in order to declare 800 mg as the MTD (if no more than 1/6 patients experience a DLT).

If no DLT is observed at 2400 mg (Dose Cohort 4), dose escalation will be stopped. The proposed highest dose level (2400 mg) will be declared the RP2D.

There will be a temporary halt for enrollment after the first 3 patients are enrolled in each cohort until the SSC clears that the dose level is safe to continue the dose escalation.

During the SSC meeting for NOX66 dose escalation decision, the safety and tolerability of both EBRT doses (8 Gy and 20/25 Gy) will also be evaluated.

DLT monitoring will be applicable for all patients enrolled in each cohort, including patients enrolled for the purpose of PK analysis; as well as the decision rule for the additional PK patients (i.e., stopping dose escalation).

**Part 2 (Dose Expansion)**

Part 2 will be expanded to enroll additional patients with mCRPC (Arm 1), BC and NSCLC (Arm 2). All patients will be treated with NOX66 RP2D along with low-dose EBRT (8 Gy or 20/25 Gy given as 1 or 5 fractionated doses, respectively). Approximately 40 patients in Arm 1 and 24 to 30 patients in Arm 2 will be enrolled.

**Eligibility Criteria:**

**Inclusion Criteria**

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

**Informed Consent**

1. Patient is capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.

**Type of Patient and Disease Characteristics**

2. Patient has a minimum life expectancy of 6 months.
3. Patient is 18 years or older at the time of signing the informed consent.
4. Histological or cytological confirmation of prostate cancer, BC, NSCLC and any other solid tumors.
5. Confirmed metastatic disease by imaging (e.g., bone scans, X-rays, ultrasound, computerized tomography, magnetic resonance imaging).
6. Documented disease progression (e.g., based on radiographic imaging, PSA or other clinical parameters) following first or later lines of anticancer systemic treatment.
7. Patient is eligible for low-dose EBRT for at least one lesion.
8. Patients with prior RT are eligible, only if there is no potential for field overlap between the prior RT and the planned RT.
9. For patients with BC or NSCLC: Patient must have at least one measurable lesion as per RECIST v1.1 (in Part 2 only).
10. Patient has Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
11. Adequate bone marrow function defined as:
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L.
    - Platelet count $\geq 100 \times 10^9$/L.
    - Hemoglobin $\geq 9.0$ g/dL (with or without transfusion).
12. Adequate renal function defined as:
    - Creatinine clearance as measured by the Cockcroft-Gault equation > 30 mL/min.

13. Adequate liver function defined as:

- Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN; patients with confirmed Gilbert's syndrome may be included in the study).
- Aspartate aminotransferase/alanine aminotransferase ≤ 2.5 × ULN (or ≤ 5 × ULN in patients with liver metastasis). Elevated alkaline phosphatase is not exclusionary if due to the presence of bone metastasis and liver function is otherwise considered adequate in the Investigator's judgement.

**Metastatic Castration-resistant Prostate Cancer**

14. Baseline testosterone levels ≤ 14.4 ng/dL and ongoing medical castration must be maintained throughout the duration of the study.
15. Patient has evidence of symptomatic and/or progressive disease. Progressive disease is defined as any one of the following:

- Radiographic disease progression in soft tissue (nodule or visceral metastasis) and/or bone with or without PSA progression. Objective evidence of increase in radiographic lesions or the appearance of 2 or more new lesions
- Prostate-specific antigen progression: At least 3 consecutive rising PSA levels (≥ 2 to 5 ng/mL) separated by at least 1 week, with castrate levels of testosterone.

**Breast Cancer Patients**

16. Known hormone receptor status (estrogen receptors/progesterone receptors or estrogen receptors alone). Breast cancer patients are allowed to be on background hormonal treatment.

**Contraception**

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

NOTE: The reliability of sexual abstinence for male or female enrollment eligibility needs to be evaluated in relation to **the duration of the clinical study and the preferred and usual lifestyle of the patient**. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

Male Patients:

17. Patient must have had a vasectomy or must agree to use a highly effective contraception as detailed in Section 10.4 of this protocol during the treatment period and for at least 3 months after the last dose of study drug and refrain from donating sperm during this period.

Female Patients:

18. A female patient is eligible to participate if she is not pregnant (see Section 10.4), not breastfeeding, and at least one of the following conditions applies:

    - Not a woman of childbearing potential (WOCBP) as defined in Section 10.4.

    OR

    - A WOCBP who agrees to follow the contraceptive guidance in Section 10.4 and not to donate ova during the treatment period and for at least 3 months after the last dose of study drug.

**Exclusion Criteria**

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

**Medical Conditions**

1. Patient has tumor involvement of the central nervous system.
2. Impaired cardiac functioning or clinically significant cardiac disease, including the following:

    - Acute myocardial infarction or unstable angina pectoris ≤ 6 months prior to starting study drug.
    - Corrected QT interval using Fridericia's formula > 470 msec on screening ECG (average of triplicate measurement will be used).
    - Uncontrolled clinically significant cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded).

      NOTE: Patients with a history of coronary artery disease, revascularization and/or stable coronary artery disease are not excluded.

3. Uncontrolled hypertension despite two concomitant antihypertensive therapies, defined as supine systolic blood pressure ≥ 150 mmHg or diastolic blood pressure > 100 mmHg based on a mean of three measurements at approximately 2-minute intervals.
4. Patients who have had a colectomy (total or left hemicolectomy) with re-anastomosis.
5. Patients for whom administration of the suppositories are likely to cause pain or difficulties in absorption (e.g., inflamed hemorrhoids, fissures or lesions of the anus or rectum).
6. Patients with fecal impaction or uncontrolled irritable bowel disease.
7. Patients with inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) will be excluded, even if the condition is well controlled.

8. Active or chronic infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C. Screening of patients with serology testing for these viruses is not required. However, patients who have a past history of viral hepatitis or in whom there is a current suspicion of viral hepatitis will have serology testing for hepatitis B and hepatitis C performed to determine whether there is any current evidence of ongoing infection with these viruses. Patients considered to be at risk for HIV infection should have HIV testing performed. If the test result is negative, the patient will be allowed to participate in the study.

   NOTE: Patients with chronic HIV infection, on ongoing treatment with anti-viral medications, who have an undetectable viral load are not considered to be infectious and can be included in this study.

9. Any other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding that, in the Investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect the interpretation of the results, render the patient at high risk from treatment complications or interferes with obtaining informed consent.
10. Patients with oligometastatic disease (fewer than 5 metastatic lesions) amenable to standard therapy will be excluded.
11. Major surgery within 4 weeks or minor surgery or biopsy within 1 week of the first dose administration.
12. Patients who have had RT to the region of the rectum or will require RT to the region of the rectum during the trial.

    NOTE: Metastatic castration-resistant prostate cancer [mCRPC] patients who have received prior prostate or prostate fossa radiation and radiation to nearby lymph nodes, where the rectum is not the target, can be included in this study.

**Prior/Concomitant Therapy**

13. Uncontrolled active infection requiring intravenous antibiotic, antiviral or anti-fungal medications within 14 days before the first dose administration. Infections (e.g., urinary tract infection) controlled on concurrent anti-microbial agents and anti-microbial prophylaxis per institutional guidelines are acceptable.
14. Receiving or having received anticancer treatment within the following period prior to the first dose administration:

    - Cytotoxic treatment: 3 weeks.

- Non-cytotoxic drugs, including small molecule investigational products: 3 weeks or 5 terminal half-lives from plasma (whichever is the longest).
- Biological products including investigational immune-oncology agents: 4 weeks.
- Radiation with a limited field for palliation: 4 weeks.
- Radiation to > 30% of the bone marrow: 4 weeks.
- Lung radiation: 60 days.

15. Patient has received corticosteroids at a dose of > 10 mg prednisone/day or equivalent for any reason within 4 weeks prior to receiving the first dose administration.
16. History of hypersensitivity to active or inactive excipients of study drug or drugs with a similar chemical structure or class to the study drug.

**Other Exclusions**

17. Patient is not willing to use suppositories.
18. Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.
19. Patient has a positive reverse transcription polymerase chain reaction (RT-PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prior to Screening or enrollment, or has clinical signs and symptoms consistent with SARS-CoV-2 infection; e.g., fever, dry cough, dyspnea, sore throat, fatigue or positive SARS-CoV-2 test result within 2 weeks prior to Screening. Patients who had symptomatic coronavirus disease 2019 (COVID-19) less than 1 month prior to Screening will be excluded. If a patient has had a severe course of COVID-19 (extracorporeal membrane oxygenation, mechanically ventilated) within 4 weeks of Screening, or have any sequelae of infection or ongoing infection, the patient will also be excluded. If the patient has had recent (within previous 14 days) exposure to someone who has COVID-19 symptoms, been in contact with someone who has tested positive for COVID-19 or visited a COVID-19 treatment facility, the patient may be re-evaluated for participation in the study after undergoing an isolation period of at least 10 days and having a negative SARS-CoV-2 RT-PCR test prior to enrollment.

**Disclosure Statement:**

This is an open-label, multicenter, sequential 2-part treatment study (Part 1 and Part 2).

**Number of Arms:**

The study will include 4 dose cohorts (Part 1) and 2 treatment arms (Part 2).

**Number of Patients:**

The sample sizes selected for this study are as follows:

- Part 1 (Dose Escalation): Up to 30 patients will be enrolled in Part 1, in cohorts of 3 to 6 patients (Dose Cohort 1) or 3 to 8 patients (Dose Cohorts 2 to 4) at each specified dose.
- Part 2 (Dose Expansion): A total of 40 patients with mCRPC will be enrolled in Arm 1 and 24 to 30 patients (12 to 15 patients per tumor type [BC and NSCLC]) will be enrolled in Arm 2.

**Dosing Groups and Duration:**

- Part 1: Eligible patients with any solid tumor will be enrolled in one of 4 dose cohorts:
  - Dose Cohort 1: 800 mg NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on the number of fractions to be administered). From Cycle 2 onwards, 800 mg NOX66 will be administered on Days 1 to 7.
  - Dose Cohort 2: 1200 mg NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, 1200 mg NOX66 will be administered on Days 1 to 7.
  - Dose Cohort 3: 1600 mg NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, 1600 mg NOX66 will be administered on Days 1 to 7.
  - Dose Cohort 4: 2400 mg NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, 2400 mg NOX66 will be administered on Days 1 to 7.
- Part 2: Eligible patients will be enrolled in 1 of 2 treatment arms:
  - Arm 1 – patients with mCRPC: RP2D NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, RP2D NOX66 will be administered on Days 1 to 7.
  - Arm 2 – patients with BC and NSCLC: RP2D NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, RP2D NOX66 will be administered on Days 1 to 7.

Patients will have a rest period (no NOX66 administration) on Days 15 to 21 of Cycle 1 and Days 8 to 14 of Cycle 2 onwards (Parts 1 and 2).

**Study Assessments:**

Efficacy will be assessed by evaluating the change from baseline PSA for patients with mCRPC. For all patients, DCR (as measured by complete response [CR], PR and SD) will also be evaluated based on change from baseline imaging using RECIST v1.1 criteria. Bone lesions will be evaluated using Prostate Cancer Working Group 3 (PCWG-3) criteria. Other assessments to be performed during this study are ECOG scores, pain severity, and Patient Reported Outcomes. Efficacy will also be evaluated by examining skeletal-related events (SREs), symptomatic skeletal events (SSEs), progression-free survival (PFS), overall survival (OS), and objective response rate.

Safety and tolerability of NOX66 and separately for both doses of EBRT (8 Gy or 20/25 Gy) will be determined by AEs, treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital signs, 12-lead ECGs and physical examinations. The study will also evaluate DLTs during Cycle 1 of Part 1.

Plasma PK analysis for idronoxil and selected metabolites will be performed for Part 1 (all patients) and Part 2 (first 10 patients enrolled for each tumor type).

Changes from baseline in the lipidomic profile, plasma levels of cytokines and chemokines (all sites), and circulatory tumor deoxyribonucleic acid (ctDNA; all patients participating at pre-selected sites only) will be assessed (Parts 1 and 2).

**Statistical Analyses:**

The main aims of the study are to assess the safety, tolerability, efficacy, PK and PD profiles of idronoxil (and selected metabolites) and EBRT in patients with prostate cancer and other solid tumors.

Continuous data will be summarized using the number of patients (n), mean, standard deviation, median, $25^{th}$ and $75^{th}$ percentiles, minimum and maximum. Categorical data will be summarized using frequency tabulations (number and percentage of patients).

Baseline will be defined as the last measurement obtained prior to the first administration of NOX66.

Disposition of patients will be listed and summarized. Patient demographics, baseline characteristics, concomitant medications and exposure to study drug will be listed and summarized for each study part by dose cohort (Part 1) or treatment arm (Part 2) using appropriate descriptive statistics.

**Primary Endpoint Analyses**

The primary endpoint for Part 1 (dose escalation) is the number of DLTs, which will be used to estimate the MTD and select the RP2D. This will be determined by the dose level at which no more than 1 out of 6 patients experiences a DLT during Cycle 1. For assessment of DLTs, toxicities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v22.0 or higher and graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. The number of DLTs experienced by a patient will be summarized by DLT type for each dose cohort and DLT events will be listed by patient. The listing will include the description, severity and relationship of the events to study drug.

The primary endpoint for Part 2 Arm 1 (mCRPC patients) is the proportion of patients who achieve ≥ 30% reduction in PSA from baseline at the end of Cycles 3 and 6. Plasma levels of PSA will be collected on Day 1 of Cycles 1 to 5, every second cycle thereafter (i.e., Cycles 7, 9, 11 etc.), at the EOT/ED Visit and at the 6-, 9- and 12 month Follow-up Visits for all patients including those that discontinued for any reason other than disease progression. The number and proportions of patients with a ≥ 30% reduction in PSA levels from baseline to the end of Cycles 3 and 6 (primary endpoint) and change from baseline at any time point (secondary endpoint) will be presented for Treatment Arm 1 along with the corresponding exact 95% confidence interval (CI; Clopper-Pearson).

The primary endpoint for Part 2 Arm 2 (BC and NSCLC patients) is DCR assessed by determining the percentage of patients with the best overall response of CR or PR at any time plus SD from the first dose administration until disease progression, death due to any cause or the start of new anticancer therapy, respectively. RECIST v1.1 criteria will be applied to assess CR, PR and SD. Disease control rate will be presented for Treatment Arm 2 along with the corresponding exact 95% CI (Clopper-Pearson). Tumor imaging and disease response assessments will be performed for up to 12 months after the last dose of study drug until disease progression, withdrawal of consent, initiation of new anticancer therapy, the patient is lost to follow-up or death, whichever comes first.

**Secondary Endpoint Analyses**

- Safety Analysis
  Safety profiles will be summarized by NOX66 dose cohort and separately by EBRT dose cohort (Part 1) or treatment arm and separately by EBRT dose cohort (Part 2) and will be based on the Safety Analysis Set. Adverse events will be coded using the MedDRA v22.0 or higher and will be graded according to the NCI-CTCAE v5.0. Treatment-emergent AEs are defined as those AEs that either start or worsen in severity on or after the date of first administration of study drug and on or before 30 days after the last dose of study drug. Treatment-emergent AEs will be summarized by severity grade and relationship to study drug. Serious AEs, serious TEAEs and TEAEs leading to discontinuation of study drug or to death will be presented. Changes in clinical laboratory values, vital signs, ECGs and physical examinations will be summarized over time.
- Efficacy Analysis
  Efficacy analysis will be conducted for the patients enrolled to Part 1 and Part 2 of the study. Results will be summarized by dose cohort (Part 1) or treatment arm (Part 2).
  - PSA samples (patients with mCRPC) will be collected on Day 1 of Cycles 1 to 5, every second cycle thereafter (i.e., Cycles 7, 9, 11, etc.), at the EOT/ED Visit and at the 6-, 9- and 12-month Follow-up Visits for all patients including those that discontinued for any reason other than disease progression. A PSA response will be considered as a PSA value reduction ≥ 30% from baseline at the end of Cycles 3 and 6. A PSA reduction from baseline at any time point will also be assessed as a secondary objective.
  - Overall response rate, defined as the percentage of patients with CR and PR, will be assessed based on change from baseline imaging (RECIST v1.1 and PCWG-3 criteria for measurable or evaluable lesions). The number and proportion of responders (CR and PR) will be presented along with the exact 95% CI (Clopper-Pearson) for the time points after Day 1. Tumor imaging assessment will be continued as scheduled for the patients who are discontinued from the study for reasons other than disease progression. The best overall response (CR, PR, SD or progression) will be summarized.
  - Change from baseline in ECOG, pain severity and pain interference with daily activities, and dose and frequency of morphine administration and analgesic use will be summarized over time. The number and proportion of patients with a pain response (≥ 2-point reduction in pain severity and no additional opioid use) will be summarized over time along with the exact 95% CIs (Clopper-Pearson). The number and proportion of patients with SREs and/or SSEs will be summarized at each time point and presented along with the exact 95% CI (Clopper-Pearson).

- Scale measures from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients (EORTC-QLQ-C30), Brief pain inventory-short form (BPI-SF), Patient Experience Questionnaire (PEQ), and Functional Assessment of Cancer Therapy – Prostate (FACT-P; mCRPC patients only) will be summarized for all patients by dose at each visit as well as the change from baseline to each visit.
- Survival functions will be computed for OS, PFS and PSA reduction/progression (for Part 2, Arm 1 only) using the Kaplan-Meier method. Estimates of median survival times will be presented along with 2-sided 95% CIs. The $25^{th}$ and $75^{th}$ percentiles and the range (minimum, maximum) will be presented as well.
- Duration of response is defined as the time from the first documented overall response of CR, PR or SD to the first documented overall response of progressive disease. This will be estimated using the Kaplan-Meier method. Estimates of median survival times will be presented along with the two-sided 95% CI. The $25^{th}$ and $75^{th}$ percentiles and range (minimum, maximum) will also be presented.

- <u>Pharmacokinetic Analysis:</u>
  Plasma samples will be assayed for idronoxil and up to 7 selected metabolites by validated high-performance liquid chromatography and mass spectrometry methodology. Individual plasma concentration-time data and plasma PK parameters will be summarized using descriptive statistics by treatment day and sampling time for idronoxil and the 7 detectable metabolites (GIS/SIG, IG, GI, IS, SI, SIS, and GIG). Plasma PK parameters will be determined by noncompartmental analysis for idronoxil and selected metabolites and will be summarized by dose and treatment day.
  - The following PK parameters will be estimated for idronoxil and the selected metabolites following the morning dose on Days 1, 6 and 14 of Cycle 1, as data permit: $C_{max}$, $C_{min}$ (predose), $T_{max}$, $AUC_{(0-t)}$, $AUC_{(0-6)}$, $AUC_{(0-12)}$, $AUC_{(0-inf)}$ and $t_{½}$.
  - Dose proportionality will be assessed for $C_{max}$, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-6)}$, and $AUC_{(0-12)}$ on Days 1, 6 and 14 of Cycle 1 for the parent compound.
  - If data permits, accumulation ratios will be calculated for parent compound and selected metabolites for $C_{max}$, $C_{min}$, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-6)}$, and $AUC_{(0-12)}$ for Days 6 and 14 of Cycle 1 (e.g., Day 14/Day 1 and Day 6/Day 1) and Day 8 of Cycles 2 and 3.
  - The metabolite to parent ratios will be calculated (as data permit) for Days 1, 6 and 14 of Cycle 1, for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-6)}$, and $AUC_{(0-12)}$ and for single time points on Day 1 of Cycles 2 and 3.

Concentration and PK parameter data will be listed, summarized and plotted.

There are no formal PK parameters for concentration data from Cycles 2 and 3 because these are single time points. However, metabolite to parent ratios will be explored.

Exploratory analyses of the relationship between plasma concentrations of parent drug and selected metabolites and/or PK parameters and AEs or PD biomarkers may be assessed by graphical methods and special summary tables. Exposure-response relationship may also be explored.

- Pharmacodynamic Biomarker Analysis:
  Plasma levels of cytokines and chemokines will be evaluated as part of the PD biomarker analysis. Using the plasma samples, analysis will be performed for ctDNA and lipidomic profiling (capturing over 300 lipid species as determined by liquid chromatography-tandem mass spectrometry). Absolute and change from baseline results of biomarker analysis will be summarized descriptively and also presented on a plot.

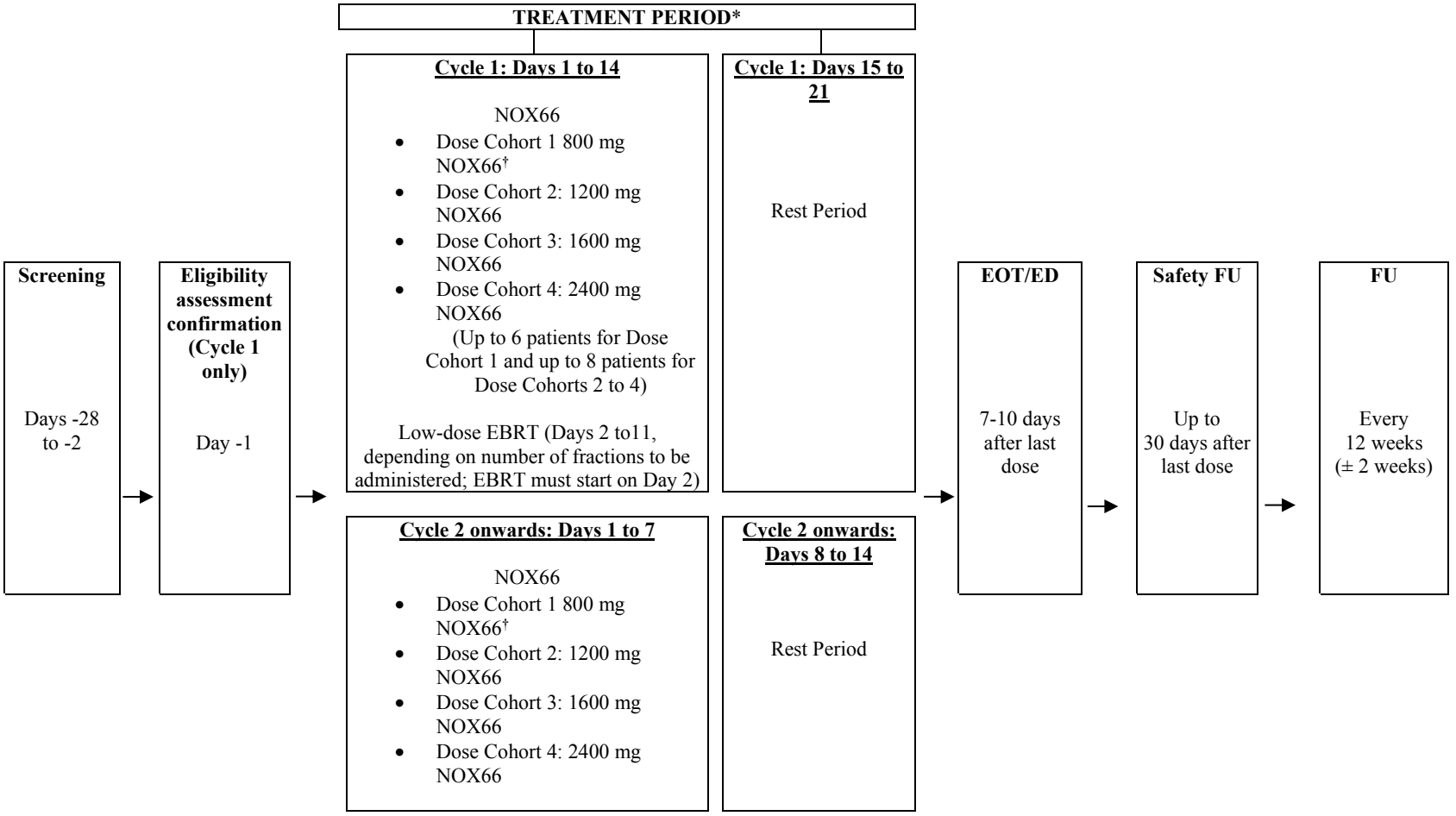
All statistical analysis will be performed using Statistical Analysis Software® Version 9.3 or higher. Further details regarding statistical analyses will be provided in the statistical analysis plan.

**Data Monitoring Committee:**

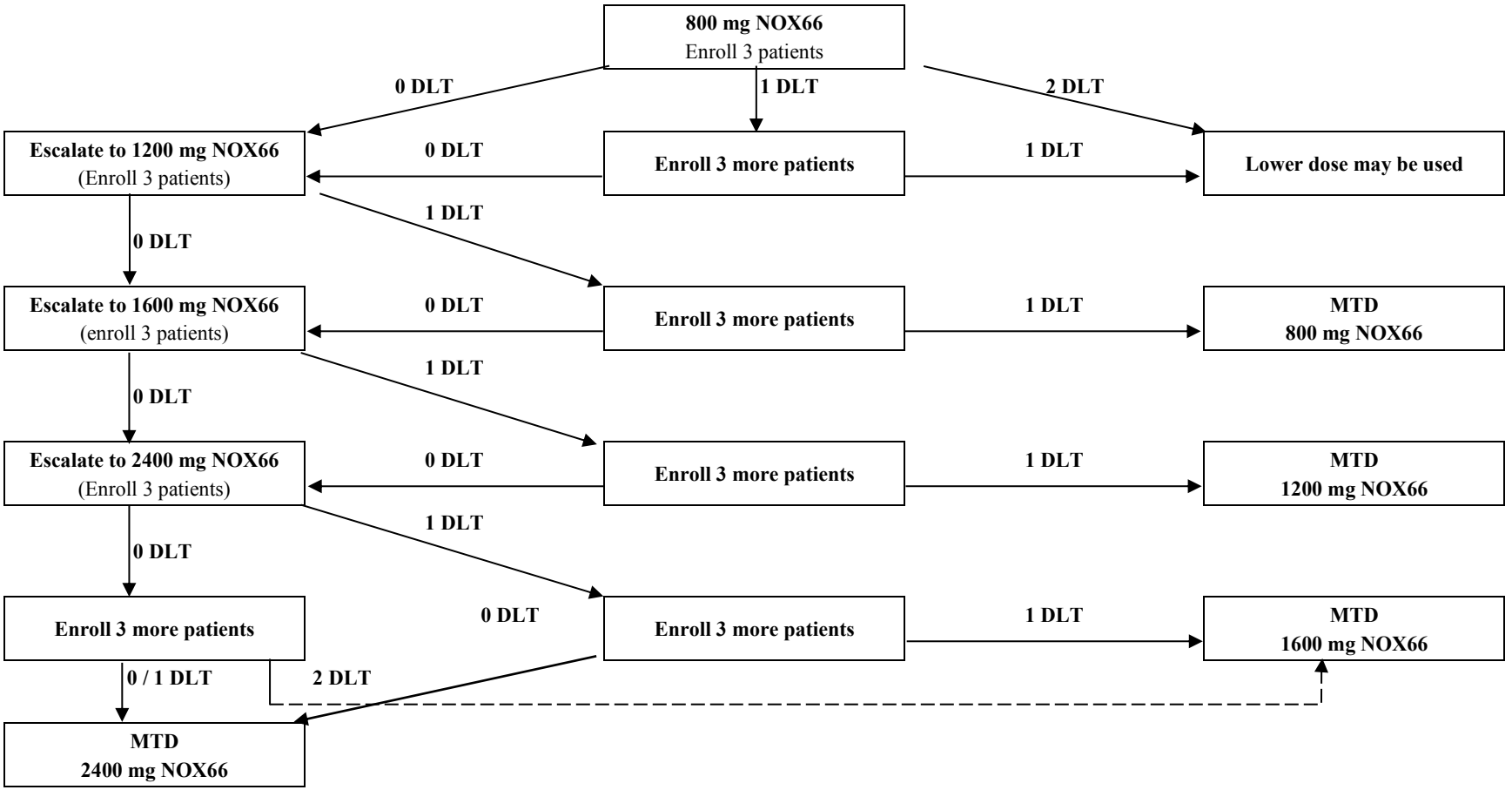
A Data Monitoring Committee will not be appointed. Patient safety and scientific integrity of the study will be monitored by the SSC.

## 1.2 Schema

**Figure 1–1: Study Design: Part 1**



**Dose Escalation between Dose Cohorts 1 to 4**




DLT = dose-limiting toxicity; EBRT = external beam radiotherapy; ED = early discontinuation; EOT = end of treatment; FU = Follow-up Visit; MTD = maximum tolerated dose

See Section 4.1.1 and Section 7.1.2.2 for details on assessment of DLTs.

* NOTE: Patients will receive the study drug until disease progression, unacceptable toxicity, withdrawal of consent, start of new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by the Sponsor.

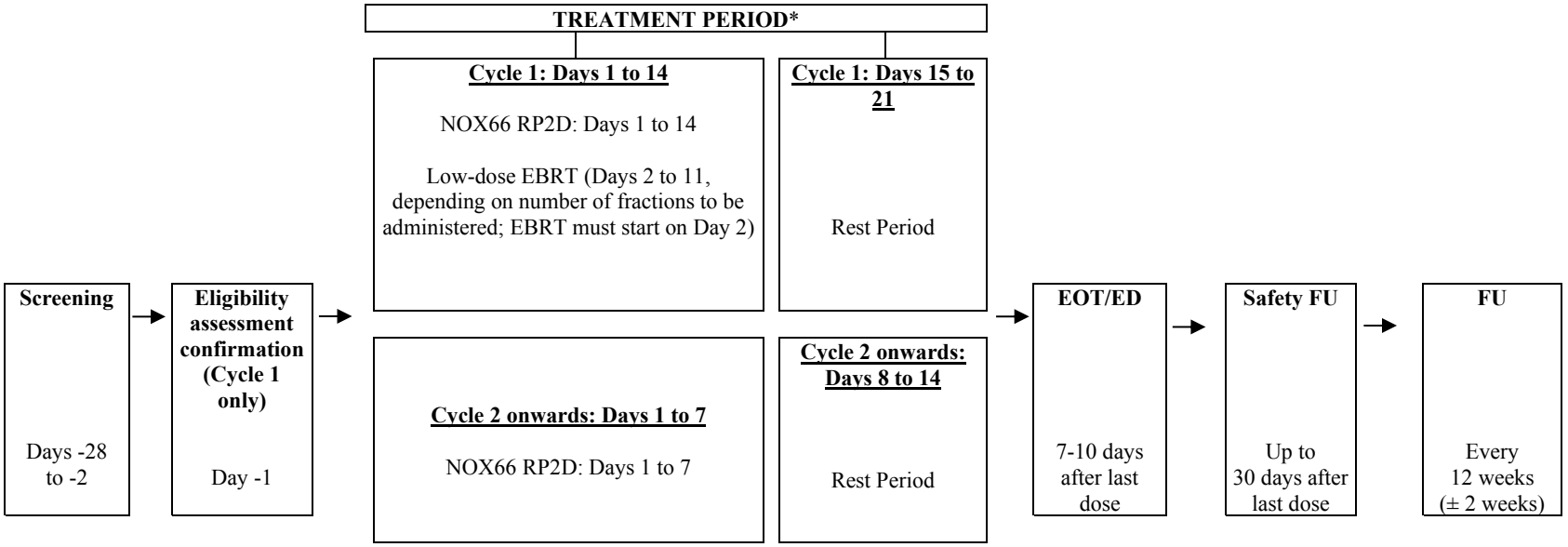
† Only 3 patients will be enrolled in Dose Cohort 1 (800 mg NOX66), unless there is a DLT. If a DLT occurs, up to a maximum of 3 additional patients may be enrolled. Additional patients will not be enrolled in Dose Cohort 1 for PK analysis.

Patients who are considered evaluable for dose escalation review are 1) patients who have not experienced a DLT and has received at least 80% of the planned daily dose and completed all safety evaluations; 2) patients who developed DLT during the 21-day treatment cycle (Cycle 1). For each dose cohort, at least 3 evaluable patients are required for DLT evaluation and to make a decision on dose escalation.

End of Treatment (EOT) Visit occurs 7 to 10 days after the last dose of study drug. If patients discontinue the study early (Early Discontinuation [ED]), they will have an ED Visit within 7 to 10 days after the last dose of study drug.

Once a patient completes or discontinues study drug, he/she will be followed up every 12 weeks (± 2 weeks) after the last dose of study drug for disease progression up to 12 months, and for safety until death or the patient is lost to follow-up.

**Figure 1–2: Study Design: Part 2**




BC = breast cancer; EBRT = external beam radiotherapy; ED = early discontinuation; EOT = end of treatment; FU = Follow-up Visit; mCRPC = metastatic castration-resistant prostate cancer; NSCLC = non-small-cell lung cancer

Patient population:

- Arm 1: mCRPC patients only (40 patients)
- Arm 2: Patients with BC and NSCLC (24 to 30 patients [12 – 15 patients per tumor type])

End of Treatment (EOT) Visit occurs 7 to 10 days after the last dose of study drug. If patients discontinue the study early (Early Discontinuation [ED]), they will have an ED Visit within 7 to 10 days after the last dose of study drug.

Once a patient completes or discontinues study drug, he/she will be followed up every 12 weeks (± 2 weeks) after the last dose of study drug for disease progression up to 12 months, and for safety until death or the patient is lost to follow-up.

* NOTE: Patients will receive the study drug until disease progression, unacceptable toxicity, withdrawal of consent, start of new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by the Sponsor.

## 1.3 Schedule of Activities

### Table 1-1 Schedule of Activities (SoA) – Part 1 and Part 2

| Procedure/Assessment | Screening | Cycle 1† | | | | | |
|---|---|---|---|---|---|---|---|
| | | Treatment Period | | | | | Rest Period |
| Day(s) | -28 to -2 | -1 | 1 | 2 to 7 | 8 to 13 | 14 | 15 to 21 |
| Week(s) | -4 to 0 | | 1 | | 2 | | 3 |
| Informed consent [c] | X | | | | | | |
| In-house stay (optional) | | | X | | | | |
| Inclusion/exclusion criteria | X | X | | | | | |
| Patient Diary [d] | | | X | X | X | X | |
| Phone call [e] | X | X | X | X | X | X | X |
| **Routine Clinical Procedures** | | | | | | | |
| Demographics | X | | | | | | |
| Medical history (including any available historical genetic assays conducted to identify genetic variations [all patients] and Gleason score for mCRPC patients only) [f] | X | X | | | | | |
| Physical examination [g] | X | | X | | | | |
| Height and weight [g] | X | | | | | | |
| Vital signs [h] | X | | X | X | | X | |
| ECG [i] | X | | X | X | | X | |
| Prior and concomitant medications [j] | X | X | X | X | | X | |

| Procedure/Assessment | Screening | Cycle 1[†] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Treatment Period | | | | | Rest Period |
| Day(s) | -28 to -2 | -1 | 1 | 2 to 7 | 8 to 13 | 14 | 15 to 21 |
| Week(s) | -4 to 0 | | 1 | | 2 | | 3 |
| **Routine Safety Measure** | | | | | | | |
| Urinalysis [k] | X | | X | X | | X | |
| Hematology [k, l] | X | | X | X | | X | |
| Clinical chemistry [k, m] | X | | X | X | | X | |
| Coagulation [k, n] | X | | X | X | | X | |
| Testosterone (mCRPC) [o] | X | | X | | | | |
| Serology screen [p] | X | | | | | | |
| SARS-CoV-2 screen (optional; at Investigator's discretion) [q] | X | | | | | | |
| FSH testing [r] | X | | | | | | |
| Pregnancy test [s] | X | | X | | | | |
| Adverse event [t] | X | X | X | X | | X | |
| **Efficacy Measurements** | | | | | | | |
| PSA [u] | X | | X | | | | |
| Tumor imaging (RECIST v1.1) CT/MRI [v] | X | | | | | | |
| Bone scan (PCWG-3) [v] | X | | | | | | |
| SRE and SSE evaluation | X | X | X | X | | X | |
| ECOG performance status | X | | X | | | | |
| EORTC-QLQ-C30 [w] | X | | | | | | |
| BPI-SF questionnaire [w] | X | | | | | | |
| FACT-P (mCRPC patients only) [w] | X | | | | | | |
| PEQ [x] | | | | X | | | |
| Survival status [y] | | | | | | | |
| **Pharmacokinetic Measurement** | | | | | | | |
| Blood sample for PK [z] | | | X | X | | X | X |

| Procedure/Assessment | Screening | Cycle 1[†] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Treatment Period | | | | | Rest Period |
| **Day(s)** | **-28 to -2** | **-1** | **1** | **2 to 7** | **8 to 13** | **14** | **15 to 21** |
| **Week(s)** | **-4 to 0** | | **1** | | **2** | | **3** |
| **Pharmacodynamic Biomarker Assessment** | | | | | | | |
| Blood sample for biomarkers [aa] | X | | X | | | | X [z] |
| Archived tissue collection if available (Optional) [bb] | X | | | | | | |
| Fresh tissue biopsy after Cycle 3 treatment (Optional) [bb] | | | | | | | |
| **Treatment Administration** | | | | | | | |
| NOX66 [cc] | | | X | X | X | X | |
| EBRT (1-10 days) [dd] | | | | X | | | |

| Procedure/Assessment | Cycle 2 Onwards† | | | | | | | | | | EOT/ED [a] (7-10 days after last dose) | Safety Follow-up (Up to 30 days after last dose) | Follow-up [b] (Every 12 weeks [± 2 weeks]) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | | | 3‡ | | | 4§ | | | 5 onwards* | | | |
| | Treatment Period | | Rest Period | Treatment Period | | Rest Period | Treatment Period | | Rest Period | | | | |
| **Day(s)** | **1** | **2 to 7** | **8 to 14** | **1** | **2 to 7** | **8 to 14** | **1** | **2 to 7** | **8 to 14** | **1** | | | |
| **Weeks** | **4** | | **5** | **6** | | **7** | **8** | | **9** | **10** | | | |
| Informed consent [c] | | | | | | | | | | | | | |
| In-house stay | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | | | | | | | | | | | | | |
| Patient Diary [d] | X | X | | X | X | | X | X | | X | | | |
| Phone call [e] | X | X | X | X | X | X | | | | X | X | X | X |
| **Routine Clinical Procedures** | | | | | | | | | | | | | |
| Demographics | | | | | | | | | | | | | |
| Medical history (including any available historical genetic assays conducted to identify genetic variations [all patients] and Gleason score for mCRPC patients only) [f] | | | | | | | | | | | | | |
| Physical examination [g] | X | | | X | | | | | | X | X | | |
| Weight [g] | X | | | | | | | | | X | | | |
| Vital signs [h] | X | | | X | | | | | | X | X | | |
| ECG [i] | X | | | X | | | | | | X | X | | |
| Prior and concomitant medications [j] | X | X | | X | X | | | | | X | X | X | X |

| Procedure/Assessment | Cycle 2 Onwards† | | | | | | | | | | EOT/ED [a] (7-10 days after last dose) | Safety Follow-up (Up to 30 days after last dose) | Follow-up [b] (Every 12 weeks [± 2 weeks]) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | | | 3‡ | | | 4§ | | | 5 onwards* | | | |
| | Treatment Period | | Rest Period | Treatment Period | | Rest Period | Treatment Period | | Rest Period | | | | |
| Day(s) | 1 | 2 to 7 | 8 to 14 | 1 | 2 to 7 | 8 to 14 | 1 | 2 to 7 | 8 to 14 | 1 | | | |
| Weeks | 4 | | 5 | 6 | | 7 | 8 | | 9 | 10 | | | |
| **Routine Safety Measure** | | | | | | | | | | | | | |
| Urinalysis [k] | X | | | X | | | | | | X | X | | |
| Hematology [k, l] | X | | | X | | | | | | X | X | | |
| Clinical chemistry [k, m] | X | | | X | | | | | | X | X | | |
| Coagulation [k, n] | X | | | X | | | | | | X | X | | |
| Testosterone (mCRPC) [o] | X | | | X | | | | | | X | X | | |
| Serology screen [p] | | | | | | | | | | | | | |
| SARS-CoV-2 screen (optional; at Investigator's discretion) [q] | | | | | | | | | | | | | |
| FSH testing [r] | | | | | | | | | | | | | |
| Pregnancy test [s] | X | | | X | | | | | | X | X | | |
| Adverse event [t] | X | X | | X | X | | | | | X | X | X | X |
| **Efficacy Measurements** | | | | | | | | | | | | | |
| PSA [u] | X | | | X | | | X | | | X | X | | X |
| Tumor imaging (RECIST v1.1) CT/MRI [v] | | | | | | | X | | | | X [b] | | X |
| Bone scan (PCWG-3) [v] | | | | | | | X | | | | X [b] | | X |
| SRE and SSE evaluation | X | | | X | | | | | | X | X | | X |
| ECOG performance status | X | | | X | | | | | | X | X | | |
| EORTC-QLQ-C30 [w] | | | | X | | | | | | X | X | | |
| BPI-SF questionnaire [w] | | | | X | | | | | | X | X | | |
| FACT-P (mCRPC patients only) [w] | | | | X | | | | | | X | X | | |
| PEQ [x] | | | | X | | | | | | | X | | |
| Survival status [y] | | | | | | | | | | | | | X |

| Procedure/Assessment | Cycle 2 Onwards† | | | | | | | | | | EOT/ED [a] (7-10 days after last dose) | Safety Follow-up (Up to 30 days after last dose) | Follow-up [b] (Every 12 weeks [± 2 weeks]) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | | | 3‡ | | | 4§ | | | 5 onwards* | | | |
| | Treatment Period | | Rest Period | Treatment Period | | Rest Period | Treatment Period | | Rest Period | | | | |
| Day(s) | 1 | 2 to 7 | 8 to 14 | 1 | 2 to 7 | 8 to 14 | 1 | 2 to 7 | 8 to 14 | 1 | | | |
| Weeks | 4 | | 5 | 6 | | 7 | 8 | | 9 | 10 | | | |
| **Pharmacokinetic Measurement** | | | | | | | | | | | | | |
| Blood sample for PK [z] | X | | X | X | | X | | | | | | | |
| **Pharmacodynamic Biomarker Assessment** | | | | | | | | | | | | | |
| Blood sample for biomarkers [aa] | | | X | | | | | | | | X | | |
| Archived tissue collection if available (Optional) [bb] | | | | | | | | | | | | | |
| Fresh tissue biopsy after Cycle 3 treatment (Optional) [bb] | | | | | | X | | | | | | | |
| **Treatment Administration** | | | | | | | | | | | | | |
| NOX66 [cc] | X | X | | X | X | | X | X | | X | | | |
| EBRT (1-10 days) [dd] | | | | | | | | | | | | | |

AE = adverse event; BPI-SF = Brief Pain Inventory – Short Form; C1D1 = Cycle 1, Day 1; COVID-19 – coronavirus disease 2019; CT = computerized tomography; d = day(s); EBRT = external beam radiotherapy; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ED = Early Discontinuation; EORTC-QLQ-C30 = Quality of life Questionnaire for Cancer Patients; EOT = End of Treatment; FACT-P: Functional Assessment of Cancer Therapy – Prostate; FSH = follicle-stimulating hormone; Gy = Gray; mCRPC = metastatic castration-resistant prostate cancer; MRI = magnetic resonance imaging; PCWG-3 = Prostate Cancer Working Group 3; PEQ = Patient Experience Questionnaire; PK = pharmacokinetics; PRO = Patient Reported Outcome; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRE = skeletal-related events; SSE = symptomatic skeletal events; WBC = white blood cell; WOCBP = women of childbearing potential

† Patients will receive the study drug from Cycle 1 Day 1 and may continue to receive the study drug until disease progression, unacceptable toxicity, withdrawal of consent, start of new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by the Sponsor.

‡ From Cycle 3 onwards, study drug for 2 cycles will be dispensed every second cycle (i.e., Cycles 5, 7, 9, 11 etc.). From Cycle 5 onwards, on-site visits will occur on a 28-day (4 weekly) basis, i.e., patients will visit the clinical unit every second cycle. After Cycle 5, the next on-site visit will therefore be Cycle 7, followed by Cycle 9, etc. until the patient completes the study treatment period or discontinues from the study, whichever comes first.

§ The procedures listed and schedule followed for Cycle 4 will be assessed at all cycles without an on-site visit (unless otherwise specified).

* The procedures detailed at Cycle 5 Day 1 will be performed for all subsequent on-site visits (unless otherwise specified). Patients will continue NOX66 administration in each cycle from Day 1 until Day 7 followed by a 7-day rest period (Days 8 to 14).

It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the timepoint. The order of assessments (as applicable to study visit) that should occur before dosing is: 1) PRO questionnaires, 2) vital signs, 3) ECG, 4) PK sampling, 5) dose administration. Blood sampling for safety laboratory assessments will be done prior to dosing. The order of assessments (as applicable to the study visit) that should occur after dosing is: 1) vital signs, 2) ECG, 3) PK sampling. All other procedures can be completed (as applicable to study visit) after the PK sample has been collected. It is critical that the patients record the time of dose in their Patient Study Drug Administration Diary for the PK assessment and the site record the time of blood sampling.

a. End of Treatment Visit (EOT) occurs 7 to 10 days after the last dose of study drug. Assessments completed within 7 days prior to the last dose of study drug do not need to be repeated. If a patient discontinues from the study early (Early Discontinuation [ED]), they will have an ED Visit within 7 to 10 days after the last dose of study drug.

b. For patients who permanently discontinue study drug for any reason other than confirmed disease progression, tumor imaging and disease response assessments will continue to be performed every 12 weeks (± 7 days) for up to 12 months after the last dose of the study drug until disease progression, withdrawal of consent, initiation of new anticancer therapy, the patient is lost to follow-up or death, whichever comes first.
   - If a patient meets disease progression during the follow-up period according to RECIST v1.1 criteria, a tumor imaging and disease response assessment is not required.
   - If a patient permanently meets clinical disease progression during the follow-up period, a tumor imaging and disease response assessment does not need to be repeated if completed ≤ 28 days after the date of clinical disease progression.
   - Patients who have met disease progression will be contacted every 3 months for survival follow-up.

c. An informed consent must be signed before any study procedures may be performed.

d. Patients will receive a Patient Study Drug Administration Diary for each cycle. Patients must record the date and time of each dose administration (Days 1 to 14 [Cycle 1] and Days 1 to 7 [Cycle 2 onwards]), as well as any missed doses.

e. All patients will be contacted by phone 1 day prior to every on-site visit for assessing signs and symptoms of coronavirus disease 2019 (COVID-19) and if they had any contact with a person who has tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients will receive a follow-up phone call 30 days after last dose to follow-up on any ongoing AEs/SAEs.

f. Medical history includes collection of data from any available historical genetic assays conducted to identify genetic variations. **For mCRPC patients only:** Gleason score assessment will also be collected as part of the medical history of the patient.

g. A complete physical examination, including weight, will be performed during the Screening Visit. A symptom-directed physical examination will be performed prior to the first dose of study drug in Cycles 1 to 3, and every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.; or within 3 days before Day 1 of the cycle) and at the EOT/ED Visit. Abbreviated physical examinations may be conducted as needed and will focus on new symptoms and will include examination of relevant systems as identified by the Investigator. Height will only be measured at Screening only. Weight will be measured at Screening,

Cycles 2, 5 and every second cycle thereafter (i.e., Cycles 7, 9, 11 etc.). Physical examinations need to include the assessment of the perineal and anal region.

h. Vital signs (oral or tympanic [both are accepted] temperature, pulse, respiratory rate and blood pressure) will be measured at Screening and during Cycle 1 at the following timepoints: predose and at 1 and 4 hours postdose on Days 1, 6 and 14. Vital signs will be measured predose on Day 1 of Cycles 1 to 3, every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.) and at the EOT/ED Visit.

i. For all patients in Part 1 and the first 10 patients of each tumor type for Part 2 who will undergo PK sampling, a series of ECGs (in triplicate, within 1 to 2 minutes apart) will be collected at Screening, and at the time points listed in Table 1-2 (Cycles 1 to 3). For patients in Part 2 who will not undergo PK sampling, a series of ECGs (in triplicate, within 1 to 2 minutes apart) will be collected at Screening and a single ECG will be collected predose (within 30 minutes prior to dosing to allow for sitting BP if needed) on Day 1 of Cycles 1 to 3.
Electrocardiograms will be taken predose (within 30 minutes prior to dosing to allow for sitting blood pressure if needed) for all patients in both study parts on Day 1 of every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.) and at the EOT/ED Visit. Electrocardiograms will be obtained after 5 minutes of rest in the supine position.

j. At each on-site visit, the study staff will question the patient about all concomitant medication used since their last on-site visit.

k. For Cycle 1 Day 1 (C1D1) predose clinical laboratory evaluations (hematology, clinical chemistry, coagulation, urinalysis) may be performed within 3 days before the first dose of study drug and these results can be used in place of the C1D1 (predose) results. Laboratory assessments for Cycle 1 Days 6 and 14 should be performed on the respective days or within 1 day before dose administration on these days. Clinical laboratory evaluations may be performed within 3 days before Day 1 of Cycles 2 and 3, every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.), and at the EOT/ED Visit.

l. Hematology: Complete blood count including hemoglobin, total white blood cell (WBC) count, differential WBC count and platelet count.

m. Clinical chemistry: Sodium, potassium, carbon dioxide, chloride, blood urea nitrogen, serum creatinine, bilirubin (total and direct), alkaline phosphatase, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total cholesterol, uric acid, calcium, magnesium, phosphate, serum glucose.

n. Coagulation parameters: Prothrombin time, international normalized ratio and activated partial thromboplastin time.

o. Testosterone levels of ≤ 14.4 ng/dL must be maintained from baseline and throughout the study. Testosterone levels will be measured at Screening, on Day 1 of Cycles 1, 2 and 3, every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.) and at the EOT/ED Visit.

p. Serology: hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody and human immunodeficiency virus. Testing only applicable to patients who have a past history of viral hepatitis or in whom there is a current suspicion of viral hepatitis, or who are considered to be at risk for human immunodeficiency virus infection.

q. Optional: SARS-CoV-2 testing to be done at Screening and additional time points. Testing to be done if medically indicated and at the discretion of the Investigator. SARS-CoV-2 testing is not required during the follow-up period. Patients will be advised about the risks of COVID-19 infection and will be questioned by phone call prior to each on-site visit to assess their health and/or contact with persons who tested positive for COVID-19 infection.

r. Postmenopausal women only.

s. Only applicable to women of childbearing potential (WOCBP). Serum pregnancy test to be performed at Screening and urine pregnancy test to be performed prior to Day 1 of Cycles 1 to 3, at every second cycle thereafter (i.e., Cycles 5, 7, 9 11 etc.) and at the EOT/ED Visit. No pregnancy testing will be performed after this period. WOCBP must continue using approved contraception methods for at least 3 months after discontinuation of the study drug. During the follow-up period, WOCBP will be questioned about their pregnancy status and use of contraception up to 3 months after last dose of study drug.

t. At each on-site visit the study staff will question the patient about all adverse events (AEs) experienced since their last on-site visit. Information on AEs and serious adverse events (SAEs) will be collected from signing of the informed consent form until 30 days after the last dose of study drug or until resolution

or stabilization of ongoing AEs deemed at least possibly related to the study drug, whichever is longer. There will be a Safety Follow-up phone call to the patient conducted 30 days after the last dose of study drug for collection of AE/SAE information.

u. Prostate-specific antigen (PSA; patients with metastatic castration-resistant prostate cancer [mCRPC] only) will have samples collected during Screening, on Day 1 of Cycles 1 to 5, every second cycle thereafter (i.e., Cycles 7, 9, 11 etc.), at the EOT/ED Visit and at the 6-, 9- and 12-month Follow-up Visits for all patients including those who discontinue the study for any reason other than disease progression. Patients who discontinue the study drug for reasons other than disease progression will continue to have PSA evaluated until disease progression, withdrawal of consent, initiation of new anticancer therapy, the end of the 12-month follow-up period or death, whichever comes first. Patients who discontinue the study drug due to disease progression do not need to provide PSA samples during the Follow-up Visits.

v. Tumor imaging and disease response assessments will be performed within 28 days prior to enrollment, every 8 weeks (± 7 days) from the first dose administration up to Week 26, and every 12 weeks (± 7 days) thereafter until disease progression, withdrawal of consent, initiation of new anticancer therapy, or death. Patients who discontinue the study drug due to any reason other than disease progression will continue to have tumor imaging and disease response assessments performed every 12 weeks (± 7 days) for up to 12 months after the last dose of study drug until disease progression, withdrawal of consent, initiation of new anticancer therapy, the patient is lost to follow-up or death, whichever comes first. Tumor imaging should ideally be performed during the rest period before the start of the next treatment cycle.

- If a patient permanently discontinues the study drug due to disease progression according to RECIST v1.1 criteria, a tumor imaging and disease response assessment is not required.
- If a patient permanently discontinues the study drug due to clinical disease progression, a tumor imaging and disease response assessment does not need to be repeated if completed ≤ 28 days of the last dose of study drug.

Patients who permanently discontinue the study drug or the follow-up period due to withdrawal of consent, Investigator to obtain tumor imaging and conduct a disease assessment at the time of the ED Visit or final Follow-up Visit if the patient agrees. A tumor imaging and disease response assessment does not need to be repeated if completed ≤ 28 days of the date of withdrawal of consent.
At a minimum, imaging of the chest, abdomen and pelvis should be performed using consistent imaging modality (computerized tomography [CT] or magnetic resonance imaging [MRI]). As far as possible, the same imaging method should be used for the patient throughout the study.

w. Questionnaire to be completed at Screening, Day 1 of Cycle 3, Day 1 of Cycle 5 followed by every 4 cycles thereafter (e.g., Cycle 9, Cycle 13 etc.) and at the EOT/ED Visit. Questionnaire to be completed prior to performing any other study visit assessments on the day of the visit.

x. Questionnaire to be completed on Day 2 of Cycle 1, Day 1 of Cycle 3 and at the EOT/ED Visit. Questionnaire to be completed prior to performing any other study visit assessments on the day of the visit (excluding predose clinical laboratory assessment for Cycle 1 Day 1 which may be completed within 3 days prior to Day 1).

y. May be an in-person visit or a phone call. Only applicable to patients who have met disease progression.

z. Pharmacokinetic samples are to be obtained on Days 1, 2, 6, 14 and 15 of Cycle 1, and Days 1 and 8 of Cycles 2 and 3. See PK sampling schedule in Table 1-3. For Part 2, PK sampling will only be performed for the first 10 patients enrolled for each tumor group (mCRPC, breast cancer or non-small-cell lung cancer).

aa. Pharmacodynamic blood samples to be collected at Screening or Cycle 1 on Days 1 and 15, prior to dosing on Day 1 of Cycle 3 (during the rest period after patients have completed 7-days of NOX66 treatment in Cycle 2, or predose on Day 1 of Cycle 3) and at the EOT/ED Visit. See PD sampling schedule in Table 1-4.

bb. Patients will be asked whether they are willing to provide both archival and fresh tissue biopsy samples OR only fresh tissue biopsy if they do not have archival tissue samples. Available archival tissue samples will only be requested if a fresh tissue biopsy is collected after Cycle 3. Provision of a fresh biopsy sample and/or an archival tissue sample is optional. See Table 1-5.

[cc.] On days when study drug and EBRT are to be administered, it is advisable that NOX66 is given at least 1 hour prior to EBRT. Twice daily of NOX66 dosing should occur at least 10 hours apart. Where 2 suppositories are administered per dosing, each suppository will be administered at least 5 minutes apart.

[dd.] The recommended dose is up to 25 Gray (Gy) radiation therapy in 1 or 5 fractionated doses over 5 to 10 days (Days 2 to 11), depending on number of fractions to be administered, e.g., 8 Gy = 1 fraction over 1 day, 20/25 Gy = 5 fractions over 5 to 10 days. EBRT must start on Day 2 of Cycle 1.

### 1.3.1 Electrocardiogram Schedule

**Table 1-2 Electrocardiogram Schedule: Part 1 (All Patients) and Part 2 (Only for First 10 Patients in Each Tumor Type)**

| Sampling Time Point | Cycle 1 Day 1 | Cycle 1 Day 2 | Cycle 1 Day 6 | Cycle 1 Day 14 | Cycle 2 Day 1 | Cycle 3 Day 1 |
|---|---|---|---|---|---|---|
| Predose | X† | X | X† | X† | X† | X† |
| 1 hour (+ 15 minutes) | X | | X | X | X | X |
| 2 hours (+ 15 minutes) | X | | X | X | | |
| 3 hours (+ 15 minutes) | X | | X | X | | |
| 4 hours (+ 15 minutes) | X | | X | X | | |
| 6 hours (+ 15 minutes) | X | | X | X | | |
| 8 hours (+ 15 minutes) | X [a] | | | | | |
| 12 hours (+ 15 minutes) | X [a] | | | | | |

† Within 30 minutes prior to dosing to allow for sitting blood pressure if needed.

[a] Only for Part 1.

NOTE: For patients who will not undergo PK sampling in Part 2 of the study, a single ECG will be collected predose on Day 1 of each cycle up to Cycle 3.

After Cycle 3 Day 1, ECGs will be taken predose (within 30 minutes prior to dosing to allow for sitting blood pressure if needed) for all patients in both study parts, on Day 1 of every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.) and at the EOT/ED Visit.

### 1.3.2 Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part 1 and Part 2

**Table 1-3 Pharmacokinetic Sampling Schedule Following Morning Dose – Part 1 (All Patients) and Part 2 (Only for First 10 Patients in Each Tumor Type)**

| Sampling Time Point | Blood Volume (mL) | Cycle 1 Day 1 | Cycle 1 Day 2* | Cycle 1 Day 6 | Cycle 1 Day 14 | Cycle 1 Day 15** | Cycle 2 Day 1 | Cycle 2 Day 8*** | Cycle 3 Day 1 [b] | Cycle 3 Day 8 [b, ***] |
|---|---|---|---|---|---|---|---|---|---|---|
| Predose (within 15 minutes prior to dosing) | 1 × 4 | X | X | X | X | X | X | X[c] | X | X[c] |
| 0.5 hour (± 5 minutes) | 1 × 4 | X | | X | X | | | | | |
| 1 hour (± 5 minutes) | 1 × 4 | X | | X | X | | | | | |
| 2 hours (± 5 minutes) | 1 × 4 | X | | X | X | | X | | X | |
| 3 hours (± 5 minutes) | 1 × 4 | X | | X | X | | | | | |
| 4 hours (± 5 minutes) | 1 × 4 | X | | X | X | | | | | |
| 6 hours (± 10 minutes) | 1 × 4 | X | | X | X | | | | | |
| 8 hours (± 15 minutes)[a] | 1 × 4 | X | | | | | | | | |
| 12 hours (± 30 minutes; Prior to evening dose) [a] | 1 × 4 | X | | | | | | | | |

[a.] Only for Part 1.

[b.] Cycle 3 Days 1 and 8 samples only for patients in Part 2.

[c.] Can be collected at home.

* Sample to be collected approximately 12 hours post Day 1 evening dose.

** Sample to be collected approximately 12 hours post Day 14 evening dose.

*** Sample to be collected approximately 12 hours post Day 7 evening dose.

**Table 1-4 Pharmacodynamic Sampling Schedule – Part 1 and Part 2 (All Patients)**

| Assay | Blood Volume (mL) | Screening/Cycle 1 Day 1 Predose [c] | Cycle 1 Day 15 | Prior to Cycle 3 [b] | End of Treatment/Early Discontinuation |
|---|---|---|---|---|---|
| Chemokines, cytokines and lipids [a] | 1 × 4 | X | X | X | X |
| Circulatory tumor DNA [a,d] | 2 × 4 | X | X | X | X |

[a] Plasma

[b] Sample should be collected after the patient has completed 7 days of NOX66 treatment in Cycle 2 and prior to dosing on Day 1 of Cycle 3.

[c] Baseline samples to be collected only after eligibility confirmation or on Day 1 prior to NOX66 administration.

[d] Only at pre-selected sites that have peripheral blood mononuclear cell isolation capabilities in Australia and the United States of America.

**Table 1-5 Optional Archival Tissue Collection and Fresh Biopsy Sampling Schedule – Part 1 and Part 2 (All Patients)**

| Assay | Screening | After Cycle 3 treatment |
|---|---|---|
| Archival tissue if available (Optional) | X | |
| Fresh biopsy (Optional) | | X |

NOTE: Available archival tissue samples will only be requested if a fresh tissue biopsy is collected after Cycle 3. Provision of a fresh biopsy sample and/or an archival tissue sample is optional.

# 2 Introduction

The term “study drug” throughout the protocol, refers to NOX66. In addition, the terms participant and patient are used interchangeably.

## 2.1 Study Rationale

Idronoxil, which is the active ingredient of the NOX66 formulation, is a synthetic flavonoid derivative of genistein that inhibits external Ecto-NOX disulfide-thiol exchanger (ENOX) 2 to induce apoptosis[2]. ENOX2 inhibition activates the sphingomyelinase pathway and deactivates the antiapoptotic protein kinase B (Akt) pathway, a key driver of radiotherapy resistance. The targeted effect on ENOX2 has the potential to limit toxicity to non-cancer cells, which preferentially express ENOX1. Previous studies have demonstrated improved radiation sensitivity in prostate cancer with flavonoid derivatives. Early studies of intravenous and oral formulations of idronoxil were hampered by limited bioavailability.[1] The Sponsor has sought to address the problem of extensive drug metabolism through the development of a rectal suppository dosage form. With blood draining from the distal part of the rectum directly into the inferior vena cava, first pass liver metabolism can be avoided. In the case of a diphenolic drug such as idronoxil, the bioavailability is augmented by the rectal mucosa being known to be devoid of transferase activity and therefore the phase II metabolism is significantly reduced. These two aspects combined are the basis for the rationale that idronoxil delivered via the rectum is subjected to less phase I and phase II metabolism than that observed for orally administered idronoxil. NOX66 is a suppository dosage form of idronoxil in a proprietary fatty base containing a surfactant. This formulation is novel in that a lipophilic active ingredient is dispersed in a lipophilic suppository base – compared with traditional suppository formulations whereby a hydrophilic base would normally be utilized. Moreover, this suppository dosage form provides a slow and sustained release of idronoxil comparable to an intravenous infusion.[2]

The first clinical study with NOX66 (NOX66-001A) was a Phase 1a/1b study in which NOX66 was evaluated both as a monotherapy and in combination with carboplatin, in patients with refractory solid tumors. Two breast cancer (BC) patients and one ovarian cancer patient enrolled in this study had reductions in target lesions size with one BC patient showing target lesion disappearance (as per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1.) at the end of the study.

The NOX66-002A study evaluated NOX66 in combination with external beam radiotherapy (EBRT) in patients with metastatic castration-resistant prostate cancer (mCRPC). Twenty-five patients received radiation therapy and 7 to 16 days of NOX66 treatment in this study.

The overall radiological assessment according to RECIST v1.1 at 3 months for 19 evaluable patients resulted in 17 patients with disease control (1 patient in the 800 mg and 2 patients in 1200 mg dose cohort with partial response [PR], 14 patients with stable disease [SD]) and 2 patients, 1 each in the 400 mg and 800 mg cohorts, respectively, with disease progression. At 6 months and of the 15 evaluable patients, 1 continued to have PR and 60% continued to have SD. There were two changes among the patients with PR in the 1200 mg cohort, with 1 patient not evaluable due to withdrawal and the other patient progressing to disease progression by RECIST v1.1 criteria while maintaining a prostate-specific antigen (PSA; 69%) and pain response (69% in overall pain score).

The overall disease control rate (DCR) at 6 months was 66.6% (10/15), with 9 patients having SD and 1 patient PR. The patient with PR also had a PSA decrease of 86% and a symptom control response of being 100% pain-free. A clinical meaningful response in a non-irradiated lesion was also observed in the same patient, with a reduction in tumor size of 26.1% from baseline at 3 months and a continued decline to 49.3% at 6 months (abscopal response). Four of 15 patients had an abscopal response in non-irradiated lesions that were outside of the radiation field.

NOX66 is designed to improve drug delivery and exposure of idronoxil to tumor cells. This Phase 1b/Phase 2a clinical study will explore higher doses of NOX66 and expand the experience of NOX66 in men with mCRPC and patients with other solid tumors to determine the recommended Phase 2 dose (RP2D) and provide preliminary evidence on overall tumor response rate, survival, symptomatic relief of pain as well as other symptoms of this disease, and effects on PSA levels (for mCRPC patients only).

## 2.2 Background

Cancer is one of the greatest health challenges of our time with prostate cancer being the second most common cancer in men. In 2018, over 1.2 million new cases of prostate cancer were diagnosed worldwide and there were 350 000 deaths due to the disease.[3]

Traditional chemotherapy and radiotherapy are destructive treatments that, while inflicting damage on cancer cells, also damage other cells in the bodies of cancer patients.[2] Genistein and its analogue daidzein are two isoflavone extracts of soy that cause a range of physiological effects, including regulation of the cell cycle and apoptosis and potent sensitization of cancer cells to radiotherapy and chemotherapy. The active ingredient of NOX66, idronoxil, is an intermediate metabolite of daidzein with greater bioavailability and anticancer activity than genistein, making it a superior drug candidate. Idronoxil has been demonstrated to have *in vitro* (half maximal inhibitory concentration [$IC_{50}$] < 10 µM) and *in vivo* activity against a broad range

of cancer cell lines from breast, cervical, colorectal, gallbladder, head and neck, leukemia, melanoma, osteosarcoma, ovarian, prostate and renal origins. By contrast, idronoxil is only mildly toxic to selected cell lines of non-cancerous origins.[2]

The binding target of idronoxil is an enzyme present on the external membrane of cancer cells known as ENOX2. This enzyme is responsible for maintaining the transmembrane electron potential (TMEP) of the plasma membrane. Inhibition of ENOX2 results in the loss of TMEP, precipitating a build-up of protons in the plasma membrane and a catastrophic series of events in the sphingomyelin pathway leading to the blockage of sphingosine-1-phosphate (S1P) production. ENOX2 is an oncogene whose expression is restricted to cancer cells. As such, idronoxil binding is highly specific to tumor cells.[2]

The primary biological effects of idronoxil stem from inhibition of the main pro-survival signaling checkpoints within the cancer cell, starting with S1P which is responsible for activation of the phosphoinositide 3-kinase (PI3) and Akt. Depending on the degree of inhibition by idronoxil, the effect ranges from cell death (variously caspase-dependent and caspase-independent apoptosis) down to sub-lethal effects (including inhibition of resistance mechanisms). Idronoxil has been shown *in vitro* to be highly selective for cancer cells and cytotoxic against multiple tumor cell lines.[2]

While idronoxil displays monotherapy cytotoxicity, NOX66 is under clinical investigation as a sensitizer of chemotherapy and radiotherapy through its ability to block resistance mechanisms including deoxyribonucleic acid repair. The degree of sensitization of chemotherapy agents, including carboplatin and doxorubicin, by idronoxil has been shown *in vitro* to be over 2000-fold.[2]

In clinical studies, orally and intravenously administered idronoxil has proven to be highly susceptible to phase II metabolism (believed to be > 99% in humans when dosed orally), resulting in extensive inactivation of the drug and limiting its clinical efficacy. NOX66 is a formulation of idronoxil designed to avoid phase II metabolism thereby conserving its bioactivity and facilitating transport and delivery of the active form of idronoxil to tumor cells. Rectal delivery reduces the possibility of phase II metabolism by bypassing first pass metabolism in the liver and avoiding the high level of phase II metabolic enzymes in the intestine.[2]

A detailed description of the chemistry, pharmacology, efficacy and safety of NOX66 is provided in the Investigator's Brochure (IB).[2]

## 2.3 Benefit/Risk Assessment

Based on Phase 1 clinical studies (Study NOX66-001A [NCT02941523] and Study NOX66-002A [NCT03307629]) with NOX66 at dosages of 400 mg, 600 mg, 800 mg and 1200 mg, treatment with NOX66 in combination with carboplatin (Study NOX66-001) in patients with solid tumors and low-dose EBRT in patients with prostate cancer (Study NOX66-002A) has been shown to be well tolerated with no emerging safety signals of concern.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of NOX66 can be found in the IB.[2]

### 2.3.1 Risk Assessment

There was one treatment-emergent adverse event (TEAE), observed in Study NOX66-001A (patients with prostate cancer, BC, ovarian cancer, and lung cancer), of moderate (Grade 2) anemia possibly related to NOX66 when dosed at 800 mg as a monotherapy. In combination with carboplatin the most common TEAEs of mild to severe anemia, neutropenia and hypocalcemia were attributed to carboplatin alone. Of the four deaths occurring during the NOX66-carboplatin treatment, sudden death, in the absence of an autopsy, was conservatively attributed to possibly related to carboplatin and all other deaths were due to disease progression.[2]

In combination with radiotherapy (Study NOX66-002A [patients with mCRPC]), AEs of mild dry mouth, stomatitis (oral mucositis) and fatigue, observed for patients receiving 400 mg, 800 mg and 1200 mg NOX66, were possibly related to the treatment.[2]

The majority of all other AEs were mild to moderate (Grades 1 to 2). Excluding serious adverse events (SAEs), Grade 3 AEs were lymphopenia, nausea, vomiting, asthenia, elevated blood alkaline phosphatase, hypocalcemia, hypophosphatemia, back pain and bone pain, and spinal pain which were reported in 4 patients. No Grade 4 AEs were reported. None of these AEs were considered related to NOX66 by the Investigator.

Pathmanandavel et al (2021) and Crumbaker (2020) conducted a Phase 1/2 trial of the combination of $_{177}$lutetium prostate-specific membrane antigen (PSMA) 617 (LuPSMA-617) in combination with NOX66 in men with end-stage mCRPC. Previous trials of lutetium PSMA in men with mCRPC had demonstrated good safety and efficacy. In this study, patients with mCRPC were administered NOX66 (400 mg to 1200 mg daily for 10 days) in combination with LuPSMA-617. Results showed similar and consistent results when compared with the safety and tolerability profile from other studies. The most frequent AEs were (Grade ≥ 2) anemia (n = 19),

fatigue (n = 9), xerostomia (n = 3), anal inflammation (n = 3), thrombocytopenia (n = 3), constipation (n = 1), and pneumonitis (n = 1).[4]

To date the administration of NOX66 has not been associated with any increase in cardiac AEs and consequently has not shown any cardiac risk from initial clinical use. There was one cardiac AE of pericarditis during NOX66 monotherapy which was of moderate severity and resolved. Cardiac monitoring and quantitative electrocardiogram (ECG) analysis before and after the period of dosing with NOX66 is included in the current study.[2]

Patients with mCRPC participating in this study may also receive androgen deprivation therapy (ADT) during the study. This standard of care (SOC) treatment has risks associated with receiving the treatment, however it is not foreseen that this SOC treatment will pose a higher risk to patients participating in this clinical study compared to other patients with mCRPC not taking part in this clinical study. Patients with BC will be allowed background hormonal therapy during this study.

During the study there is also the risk of spreading severe acute respiratory coronavirus 2 (SARS-CoV-2) which is known to be transmissible via respiratory droplets. The coronavirus disease 2019 (COVID-19) pandemic began in Wuhan, China, in December 2019 and became a global public health emergency in March 2020. Given that the study enrolls patients with cancer who are in need of treatment, the protocol allows inclusion of patients with mCRPC for whom the Investigator determined that the risk of potential exposure to COVID-19 (e.g., as a result of travel to the site and considering any other co-morbidities or risk factors the patient may have) does not outweigh the potential benefit of receiving treatment. Given that each site and/or country may be impacted differently during the COVID-19 pandemic and changes may occur at a rapid pace, each site should follow their own institutional guidelines, as well as making individual risk assessments of their sites ability to enroll and, when needed, to hold enrollment of patients.

Measures to mitigate additional risks caused by the COVID-19 pandemic include:

- The study is going to start enrolling only when the Sponsor and study site in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local authorities.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.

- Patients will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat and fatigue throughout the study. Once clinical signs of infection are reported by patients, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurements during outpatient visits will be implemented.
- Confirmation of COVID-19 infection by laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on Investigator's discretion. This would include testing at Screening and may optionally be done at additional time points if the patient has been in contact with someone who tested positive or has any signs and/or symptoms of COVID-19 infection.
- The probability of virus transmission will be controlled as much as possible by:
    - Advice for patients to adhere to local requirements for reduction of the public exposure while ambulatory.
    - All patients are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected COVID-19 disease. In addition, patients are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, patients will be referred to the local health care system for further follow-up and treatment.
    - Physical distancing and person-to-person contact restrictions will be applied during site visits.
    - Where physical distancing is not possible, personal protective equipment will be used by study patients (for example surgical face mask, and gloves) and staff (for example but not limited to masks, gloves, protectors, and medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.
- Patients will follow site policy in order to mitigate the additional risks caused by COVID-19. All medical measures, risk/benefit and restrictions associated with COVID-19 screening will be explained in the informed consent form (ICF).

### 2.3.2 Benefit Assessment

Traditional cancer treatments (e.g., chemotherapy and radiotherapy) inflict damage on both cancer cells and healthy tissue cells as it is not target-specific. In contrast, idronoxil has be shown *in vitro* to be highly selective for cancer cells and cytotoxic against multiple tumor cell lines as well as being only slightly toxic to non-cancerous cells.

A drawback observed in previous clinical studies with orally dosed NOX66 was its high susceptibility to phase II metabolism (believed to be > 99% in humans) which resulted in extensive inactivation of the drug and limited its clinical efficacy. The Sponsor has sought to address this problem through the development of a suppository dosage form for rectal administration which avoids first pass liver metabolism and reduces phase II metabolism and can lead to greater bioavailability and clinical efficacy in patients. Moreover, this dosage form provides a slow and sustained release of idronoxil compared to intravenously administered idronoxil.

This study primarily aims to evaluate the safety and tolerability of NOX66 suppository dosage form and determining the RP2D in patients with mCRPC and other solid tumors (Part 1), and determining its effect on PSA response (in patients with mCRPC) and DCR (in patients with BC or non-small cell lung cancer [NSCLC]) (Part 2). This study will further inform the dose regimen to be used in further clinical development of idronoxil as a potential target-specific treatment for various cancers including mCRPC and other solid tumors.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with NOX66 are justified by the anticipated benefits that may be afforded to patients with mCRPC and other solid tumors.

## 3 Objectives and Endpoints

**Table 3-1 Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary Objectives and Endpoints** | |
| Part 1 (Dose Escalation):<br><br>To determine the MTD and RP2D of NOX66 in combination with low-dose EBRT in patients with any solid tumor | The primary objective for Part 1 will be determined based on the count of DLTs.<br>• MTD is defined as the dose level at which no more than 1 patient out of 6 experiences a DLT at the end of Cycle 1.<br>• RP2D is the highest dose administered at which no more than 1 patient out of 6 experiences a DLT at the end of Cycle 1 and the dosage form, including the dosing frequency, is acceptable to patients. |

| Objectives | Endpoints |
|---|---|
| Part 2 (Dose Expansion):<br>Arm 1: To evaluate the effect of NOX66 on PSA response in patients with mCRPC.<br><br>Arm 2: To evaluate the effect of NOX66 on DCR in patients with BC and NSCLC. | • PSA response is defined as the proportion of patients with a reduction in PSA in plasma (ng/mL) of ≥ 30% from baseline at the end of Cycles 3 and 6.<br>• DCR is measured by the percentage of patients with a best overall confirmed response of CR or PR and SD. |
| **Secondary Objectives and Endpoints** | |
| Characterize the safety and tolerability of NOX66 | Safety and tolerability of NOX66 as determined by AEs, TEAEs, clinical laboratory evaluations, vital signs, 12-lead ECG and physical examinations. |
| Evaluate the safety and tolerability of both doses of EBRT | Safety and tolerability of both doses of EBRT as determined by AEs, TEAEs, clinical laboratory evaluations, vital signs, 12-lead ECG and physical examinations. |
| Evaluate the exposure of idronoxil | Concentration of idronoxil and selected metabolites in plasma and derived PK parameters, including but not limited to: $C_{max}$, $T_{max}$, $AUC_{(0-t)}$, $AUC_{(0-6)}$, $AUC_{(0-12)}$, $AUC_{(0-inf)}$, $C_{min}$ and $t_{½}$, as data permit. |
| Evaluate the preliminary clinical efficacy of NOX66 plus low-dose EBRT in patients with mCRPC and other solid tumors | Preliminary clinical efficacy as determined by:<br>• Change from baseline in PSA (mCRPC only) at any time point.<br>• Overall response rate assessed by RECIST v1.1 criteria (all tumor types) and PCWG-3 criteria (mCRPC).<br>• Duration of response (for patients with measurable disease).<br>• Change from baseline ECOG scores.<br>• Change from baseline in tumor size and number.<br>• PFS and OS. |
| Explore the effects of NOX66 on pain and other cancer-related signs and symptoms | Effects on pain and other cancer-related signs and symptoms as determined by:<br>• Change from baseline in pain scores based on the BPI-SF questionnaire.<br>• SREs and SSEs.<br>• Change of dose and frequency of morphine administration and analgesic use. |

| Objectives | Endpoints |
|---|---|
| Evaluate the QoL using PRO questionnaires | QoL as assessed by:<br>• Change from baseline in PEQ.<br>• Change from baseline in EORTC-QLQ-C30.<br>• Change from baseline in FACT-P (mCRPC only). |
| **Exploratory Objectives and Endpoints** | |
| Characterize the relationship between pharmacodynamic biomarkers and idronoxil plasma concentrations (if a meaningful change is observed) | • Change in biomarkers (cytokines, chemokines and ctDNA) from baseline.<br>• Change in lipid profile from baseline. |

AE = adverse event; BC = breast cancer; BPI-SF = Brief Pain Inventory – Short Form; CR = complete response; ctDNA = circulatory tumor deoxyribonucleic acid; DCR = disease control rate; DLT = dose-limiting toxicity; EBRT = external beam radiotherapy; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; MTD = maximum tolerated dose; NSCLC = non-small-cell lung cancer; OS = overall survival; PCWG-3 = Prostate Cancer Working Group 3; PEQ = Patient Experience Questionnaire; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; PRO = Patient Reported Outcome; PSA = prostate-specific antigen; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SD = stable disease; SRE = skeletal-related events; SSE = symptomatic skeletal events; TEAE = treatment-emergent adverse event

# 4 Study Design

## 4.1 Overall Design

This is a Phase 1b/Phase 2a, open-label, multicenter study to determine the safety, tolerability, RP2D, efficacy, pharmacokinetics (PK) and pharmacodynamic (PD) properties of idronoxil when rectally administered as a suppository (NOX66) to patients with any solid tumor (Part 1) and patients with mCRPC, BC and NSCLC (Part 2) who are eligible for low-dose EBRT for at least one symptomatic or minimally symptomatic lesion (for the prevention of symptoms). The study will be performed in approximately 14 sites in Australia, United States (US) and Europe. The study is divided into 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion). The study design allows an exploration of different doses of NOX66 (800 mg, 1200 mg, 1600 mg and 2400 mg) with safety monitoring to ensure the safety of the patients. A Safety Steering Committee (SSC) will review available safety data after the first cycle (21 days) of each dose cohort of NOX66 in Part 1 to determine the maximum tolerated dose (MTD)/RP2D.

In Cycle 1, NOX66 will be administered for 14 days followed by a 7-day rest period on a 21-day cycle. From Cycle 2 onwards, NOX66 will be administered for 7 days followed by a 7-day rest period on a 14-day cycle. Patients will continue to receive NOX66 on a cyclical basis until

disease progression, unacceptable toxicity, withdrawal of consent, start of a new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by the Sponsor.

The study population consist of patients with mCRPC, BC, NSCLC or other solid tumors who have failed at least one line of prior treatment and for whom, according to the Investigator, are eligible for low-dose EBRT for at least one symptomatic or minimally symptomatic lesion (for the prevention of symptoms).

The dose levels of EBRT will be either:

- 8 Gray (Gy) as a single fraction, or
- 20/25 Gy as 5 fractions given over 5 to 10 days.

The first EBRT dose fraction must be administered on Day 2 of Cycle 1 and the remaining dose fractions will be given between Day 3 and Day 11. The choice of one of the EBRT dose/fractions stated above will be at the discretion of the Investigator and will be determined by the clinical requirements of the patient. EBRT will be administered according to the institutional protocol.

Additional EBRT at the dose levels/fractions stated above may be given during the study. However, should additional EBRT be considered necessary during the study (Cycle 2 onwards), the Investigator should communicate this to the Medical Monitor for team acknowledgment since extra doses could impact study results.

The expected study duration for each patient from initial administration of NOX66 until the last study visit is determined by the number of treatment cycles each patient receives plus the follow-up period, which is from the last dose of NOX66 on study until death or the patient is lost to follow-up.

The study will finish when the last patient enrolled in Part 2 completes 6 months of treatment and all patients receiving study drug at that time will be switched to the NOX66 compassionate access program. Those patients on the compassionate access program will continue to receive NOX66 treatment until disease progression or unacceptable toxicity. The patients will be followed until death, or the patient is lost to follow-up.

There will be a Screening period of up to 27 days (Days -28 to -2). Each patient will attend the study center on Day -1 of Cycle 1 for eligibility assessments and on all PK days (Cycle 1: Days 1, 2, 6, 14 and 15; Cycles 2 and 3: Days 1 and 8). Patients in Part 1 may require an overnight stay on Day 1 of Cycle 1. On Days 1, 2, 6 and 14 of Cycle 1 and Day 1 of Cycles 2 and 3, the NOX66 morning administration will occur at the study center under medical supervision. During these days blood samples for PK analysis will be collected as per the

schedule mentioned in Table 1-3. In addition to PK samples, patients will be monitored for cardiac effects using 12-lead ECGs (Table 1-2). NOX66 will be self-administered by the patients or administered by their care giver at home on all other dosing days as well as the evening doses of NOX66 on PK days (Cycle 1: Days 2, 6 and 14; Cycles 2 and 3: Day 1). The evening dose of Day 1 of Cycle 1 (in Part 1 only) will be administered at the clinical unit. Patients or care givers should always wear gloves when handling and/or during administration of NOX66. The use of a small amount of water-soluble lubricant is advised before rectal administration. No oil- or wax-based lubricants should be used during rectal administration. Further administration instructions are provided in the "Instructions for Administration of NOX66 Suppositories" document. Patients will also attend the study center for EBRT (8 Gy or 20/25 Gy given as 1 or 5 fractionated doses, respectively) on Days 2 to 11 of Cycle 1 depending on the number of fractions to be administered. From Cycle 2 onwards only NOX66 will be administered for 7 days followed by a 7-day rest period (as indicated above). Patients with mCRPC may also receive ADT as maintenance therapy and patients with BC may receive background hormonal therapy during this study. No other anticancer therapy will be allowed during the study. Patients will have an End of Treatment (EOT) Visit within 7 to 10 days after the last dose of study drug. If a patient discontinues the study early (Early Discontinuation [ED]), the patient will have an ED Visit within 7 to 10 days after the last dose of study drug.

Patients in both study parts will be followed up by phone for AEs/SAEs for 30 days after the last dose of study drug or until resolution or stabilization of ongoing AEs/SAEs deemed at least possibly related to the study drug, whichever is longer. All patients (including patients who discontinued the study early for reasons other than disease progression) will be followed up approximately every 12 weeks (± 2 weeks) after completion of the treatment period for disease progression up to 12 months, and for safety until death, or the patient is lost to follow-up. Patients who discontinued the study early for reasons other than disease progression will attend the clinical unit for the follow-up visits. Patients will receive the study drug until disease progression, unacceptable toxicity, withdrawal of consent, initiation of new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by the Sponsor. Tumor imaging and disease response assessments will be performed for up to 12 months after the last dose of study drug until disease progression, withdrawal of consent, initiation of new anticancer therapy, the patient is lost to follow-up or death, whichever comes first.

The study will include 4 dose cohorts (Part 1) and 2 treatment arms (Part 2):

- Part 1: Eligible patients with any solid tumor will be enrolled in one of 4 dose cohorts:
  - Dose Cohort 1: 800 mg NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on the number of fractions to be administered). From Cycle 2 onwards, 800 mg NOX66 will be administered on Days 1 to 7.
  - Dose Cohort 2: 1200 mg NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, 1200 mg NOX66 will be administered on Days 1 to 7.
  - Dose Cohort 3: 1600 mg NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, 1600 mg NOX66 will be administered on Days 1 to 7.
  - Dose Cohort 4: 2400 mg NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, 2400 mg NOX66 will be administered on Days 1 to 7.
- Part 2: Eligible patients will be enrolled in 1 of 2 treatment arms:
  - Arm 1 – patients with mCRPC: RP2D NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, RP2D NOX66 will be administered on Days 1 to 7.
  - Arm 2 – patients with BC and NSCLC: RP2D NOX66 (Days 1 to 14 [Cycle 1]) + EBRT (Days 2 to 11 of Cycle 1, depending on number of fractions to be administered). From Cycle 2 onwards, RP2D NOX66 will be administered on Days 1 to 7.

Patients will have a rest period (no NOX66 administration) on Days 15 to 21 of Cycle 1 and Days 8 to 14 of Cycle 2 onwards (Parts 1 and 2).

The study schemes are provided in Figure 1–1 (Part 1) and Figure 1–2 (Part 2), and the Schedule of Activities (SoA) is provided in Table 1-1 (Parts 1 and 2).

### 4.1.1 Part 1 (Dose Escalation)

Approximately 30 patients with any solid tumor who require low-dose EBRT will be enrolled sequentially to the four planned NOX66 dose groups (Dose Cohort 1: 800 mg [3 to 6 patients]; Dose Cohort 2: 1200 mg; Dose Cohort 3: 1600 mg; Dose Cohort 4: 2400 mg [3 to 8 patients in each of Dose Cohorts 2 to 4]; total daily dose administered twice a day [BID]). At least 2 patients enrolled in Dose Cohorts 2 to 4 must have mCRPC.

The proposed dose regimen for Part 1 is given in Table 4-1. No intra-subject dose escalation is allowed.

**Table 4-1 Proposed Doses for NOX66 (Part 1)**

| | Dose Cohort | | | |
|---|---|---|---|---|
| | **1** | **2** | **3** | **4** |
| Total daily dose | 800 mg | 1200 mg | 1600 mg | 2400 mg |
| Dosing regimen | 400 mg BID | 600 mg BID | 800 mg BID | 1200 mg BID |
| Number of suppositories per day | 2 × 400 mg | 2 × 600 mg | 4 × 400 mg | 4 × 600 mg |

BID = twice daily

All patients will be closely monitored for any dose-limiting toxicities (DLTs) up to Day 21 of Cycle 1.

Dose escalation will be based on an adapted "3+3" design, where dose cohorts will be expanded for up to 6 patients (Dose Cohort 1) in the event of DLT or up to 8 patients (Dose Cohorts 2 to 4) to allow for robust estimation of PK parameters after being deemed "safe" based on the traditional "3+3" design.

At each dose level, 3 patients will initially be treated with NOX66.

- If none of the first 3 patients enrolled in Cohort 1 experience a DLT during the first treatment cycle, the dose will be escalated to the next level.
- If none of the first 3 patients experience a DLT during the first treatment cycle of Cohorts 2 to 4, then the dose level will be deemed "safe" and up to 5 additional patients will be enrolled to the current dose level for estimation of PK parameters. At the same time (with the exception of Cohort 4), the next dose level will be initiated and the first 3 patients will be enrolled to the escalated dose.
- If 1/3 patients experience a DLT, an additional 3 patients will be enrolled. If 1/6 patients experience a DLT then this dose level will be deemed "safe" and, for Cohorts 2 to 4, 2 more patients may be enrolled for estimation of PK parameters. At the same time, the next dose level will be initiated and the first 3 patients will be enrolled to the escalated dose.
- If > 1/3 or > 1/6 patients experience a DLT, then dose escalation will be halted, and the previous dose will be declared as the MTD.

If the 1200 mg dose is not tolerable (i.e., 2 or more patients with DLTs), an additional 3 patients will be enrolled in the 800 mg dose cohort in order to declare 800 mg as the MTD (if no more than 1/6 patients experience a DLT).

If no DLT is observed at 2400 mg (Dose Cohort 4), dose escalation will be stopped. The proposed highest dose level (2400 mg) will be declared the RP2D.

There will be a temporary halt for enrollment after the first 3 patients are enrolled in each cohort until the SSC clears that the dose level is safe to continue the dose escalation. During the SSC meeting for NOX66 dose escalation decision, the safety and tolerability of both EBRT doses (8 Gy and 20/25 Gy) will also be evaluated. For details on DLT evaluation, see Section 7.1.2.2.

DLT monitoring will be applicable for all patients enrolled in each cohort, including patients enrolled for the purpose of PK analysis; as well as the decision rule for the additional PK patients (i.e., stopping dose escalation).

### 4.1.2 Part 2 (Dose Expansion)

Part 2 will be expanded to enroll additional patients with mCRPC (Arm 1), BC and NSCLC (Arm 2). All patients will be treated with NOX66 RP2D along with low-dose EBRT (8 Gy or 20/25 Gy given as 1 or 5 fractionated doses, respectively).

Part 2 will enroll 2 treatment arms:

- Arm 1 (n = 40): Patients with mCRPC.
- Arm 2 (n = 24 to 30): Patients with BC and NSCLC.

## 4.2 Scientific Rationale for Study Design

Better SOC treatments for patients with prostate cancer and patients with other solid tumors, who have exhausted treatments, are needed. Based on the positive results observed in Phase 1 clinical studies with NOX66, further investigation is warranted.

The study is divided into 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion). During Part 1, four dose levels of NOX66 will be examined to determine the MTD and RP2D to be used in further clinical development of NOX66. In Part 2, the confirmed RP2D dose level will be further examined in patients with mCRPC, BC and NSCLC. Part 2 will also examine the effect of NOX66 on PSA of patients with mCRPC and the tumor response in patients with BC and NSCLC.

Radiotherapy (i.e., low-dose EBRT) will be provided to patients during this study. Low-dose EBRT is administered for the treatment of symptomatic lesions and/or to prevent asymptomatic lesions from becoming symptomatic. Low-dose EBRT (8 Gy or 20/25 Gy as 1 or 5 fractionated doses, respectively) will be administered in this study for symptom control of lesions and

prevention of signs and symptoms. The safety of the combination of NOX66 and EBRT has been tested in men with symptomatic mCRPC[1] (see IB[2] for details).

The starting dose, dose escalation decision points and patient population size are based on accepted methodology for Phase 1/Phase 2 studies.

In the previous study (NOX66-002A), the doses of 400 mg, 600 mg, 800 mg and 1200 mg of NOX66 were explored in combination with low-dose EBRT in patients with mCRPC. The highest dose tested in this study was 1200 mg and a total of 15 patients have been treated with this dose. There were no DLTs reported in that study. Based on the NOX66-002A study safety and efficacy data this planned study is designed to continue the dose escalation from 800 mg (400 mg BID) to 1200 mg (600 mg BID) to 1600 mg (800 mg BID) followed by 2400 mg (1200 mg BID), if tolerable.

In the previous trial, the total duration of NOX66 treatment was up to 16 days and low-dose EBRT of 20 Gy was given in 5 fractionated doses over 5 to 7 days. NOX66 will be administered in this planned study on a 21-day cycle basis (14 days on treatment followed by 7 days off treatment) during Cycle 1, and on a 14-day cycle basis (7 days on treatment followed by 7 days off treatment) from Cycle 2 onwards. NOX66 will be administered until disease progression, unacceptable toxicity, withdrawal of consent, start of a new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by the Sponsor.

The timings of safety and PK assessments in the study have been designed on the basis of non-clinical and clinical findings. These data will be important to evaluate exposure-response relationships for efficacy and safety in mCRPC and other tumor types.

As part of the clinical drug development program for NOX66, the Sponsor plans to include investigations into PD biomarker profiles and their relation to study drug effect at the intended dosage. These biomarkers will be derived from blood samples taken during the study. There are many potential benefits to this biomarker research, including the possibility to identify patients most likely to benefit from treatment, explain outliers and non-responders or explain adverse reactions related to study drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilized to bring better drug products to the clinic.

## 4.3 Justification for Dose

The selected starting dose, 800 mg NOX66 (total dose; 400 mg BID), has been used in a previous clinical trial (NOX66-002A) and was shown to be safe and well tolerated. This dose level is the possible lowest BID dose of NOX66.

Low-dose EBRT (8 Gy or 20/25 Gy given as 1 or 5 fractionated doses, respectively) is considered SOC in this patient population. The choice of dose/fraction is at Investigator's discretion based on patient's need. Site will need to follow institutional practice for low-dose EBRT administration.

## 4.4 End of Study Definition

Once a patient completes or discontinues study drug, he/she will be followed up every 12 weeks (± 2 weeks) after the last dose of study drug for disease progression up to 12 months, and for safety until death or the patient is lost to follow-up.

For the entire study, study completion is defined as the last visit of the last patient for any protocol related activity (last patient, last visit), including telephone contact. For individual patients, study completion is defined as the time of the patient's last data collection.

The study will finish when the last patient enrolled in Part 2 completed 6 months of treatment; all patients receiving study drug at that time will be switched to the NOX66 compassionate access program. Those patients on the compassionate access program will continue to receive NOX66 treatment until disease progression or unacceptable toxicity. These patients will be followed until death, or the patient is lost to follow-up.

# 5 Study Population

The study population will consist of patients with mCRPC, BC, NSCLC or other solid tumors who have failed at least one line of prior treatment and for whom, according to the Investigator, are eligible for low-dose EBRT for at least one symptomatic or minimally symptomatic lesion (for the prevention of symptoms).

## 5.1 Inclusion Criteria

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

**Informed Consent**

1. Patient is capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

**Type of Patient and Disease Characteristics**

2. Patient has a minimum life expectancy of 6 months.
3. Patient is 18 years or older at the time of signing the informed consent.
4. Histological or cytological confirmation of prostate cancer, BC, NSCLC and any other solid tumors.
5. Confirmed metastatic disease by imaging (e.g., bone scans, X-rays, ultrasound, computerized tomography [CT], magnetic resonance imaging [MRI]).
6. Documented disease progression (e.g., based on radiographic imaging, PSA or other clinical parameters) following first or later lines of anticancer systemic treatment.
7. Patient is eligible for low-dose EBRT for at least one lesion.
8. Patients with prior RT are eligible, only if there is no potential for field overlap between the prior RT and the planned RT.
9. For patients with BC or NSCLC: Patient must have at least one measurable lesion as per RECIST v1.1 (in Part 2 only).
10. Patient has Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
11. Adequate bone marrow function defined as:
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L.
    - Platelet count $\geq 100 \times 10^9$/L.
    - Hemoglobin $\geq 9.0$ g/dL (with or without transfusion).
12. Adequate renal function defined as:
    - Creatinine clearance as measured by the Cockcroft-Gault equation > 30 mL/min.

13. Adequate liver function defined as:

- Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN; patients with confirmed Gilbert's syndrome may be included in the study).
- Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 × ULN (or ≤ 5 × ULN in patients with liver metastasis). Elevated alkaline phosphatase is not exclusionary if due to the presence of bone metastasis and liver function is otherwise considered adequate in the Investigator's judgement.

**Metastatic Castration-resistant Prostate Cancer**

14. Baseline testosterone levels ≤ 14.4 ng/dL and ongoing medical castration must be maintained throughout the duration of the study.
15. Patient has evidence of symptomatic and/or progressive disease. Progressive disease is defined as any one of the following:

- Radiographic disease progression in soft tissue (nodule or visceral metastasis) and/or bone with or without PSA progression. Objective evidence of increase in radiographic lesions or the appearance of 2 or more new lesions.
- Prostate-specific antigen progression: At least 3 consecutive rising PSA levels (≥ 2 to 5 ng/mL) separated by at least 1 week, with castrate levels of testosterone.

**Breast Cancer Patients**

16. Known hormone receptor status (estrogen receptors/progesterone receptors or estrogen receptors alone). Breast cancer patients are allowed to be on background hormonal treatment.

**Contraception**

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

NOTE: The reliability of sexual abstinence for male or female enrollment eligibility needs to be evaluated in relation to **the duration of the clinical study and the preferred and usual lifestyle of the patient**. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

Male Patients:

17. Patient must have had a vasectomy or must agree to use a highly effective contraception as detailed in Section 10.4 of this protocol during the treatment period and for at least 3 months after the last dose of study drug and refrain from donating sperm during this period.

Female Patients:

18. A female patient is eligible to participate if she is not pregnant (see Section 10.4), not breastfeeding, and at least one of the following conditions applies:

    - Not a woman of childbearing potential (WOCBP) as defined in Section 10.4.

      OR

    - A WOCBP who agrees to follow the contraceptive guidance in Section 10.4 and not to donate ova during the treatment period and for at least 3 months after the last dose of study drug.

## 5.2 Exclusion Criteria

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

**Medical Conditions**

1. Patient has tumor involvement of the central nervous system.
2. Impaired cardiac functioning or clinically significant cardiac disease, including the following:

    - Acute myocardial infarction or unstable angina pectoris ≤ 6 months prior to starting study drug.
    - Corrected QT interval (QTc) using Fridericia's formula (QTcF) > 470 msec on screening ECG (average of triplicate measurement will be used).
    - Uncontrolled clinically significant cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded).

      NOTE: Patients with a history of coronary artery disease, revascularization and/or stable coronary artery disease are not excluded.

3. Uncontrolled hypertension despite two concomitant antihypertensive therapies, defined as supine systolic blood pressure ≥ 150 mmHg or diastolic blood pressure > 100 mmHg based on a mean of three measurements at approximately 2-minute intervals.

4. Patients who have had a colectomy (total or left hemicolectomy) with re-anastomosis.
5. Patients for whom administration of the suppositories are likely to cause pain or difficulties in absorption (e.g., inflamed hemorrhoids, fissures or lesions of the anus or rectum).
6. Patients with fecal impaction or uncontrolled irritable bowel disease.
7. Patients with inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) will be excluded, even if the condition is well controlled.
8. Active or chronic infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C. Screening of patients with serology testing for these viruses is not required. However, patients who have a past history of viral hepatitis or in whom there is a current suspicion of viral hepatitis will have serology testing for hepatitis B and hepatitis C performed to determine whether there is any current evidence of ongoing infection with these viruses. Patients considered to be at risk for HIV infection should have HIV testing performed. If the test result is negative, the patient will be allowed to participate in the study.

   NOTE: Patients with chronic HIV infection, on ongoing treatment with anti-viral medications, who have an undetectable viral load are not considered to be infectious and can be included in this study.
9. Any other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding that, in the Investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect the interpretation of the results, render the patient at high risk from treatment complications or interferes with obtaining informed consent.
10. Patients with oligometastatic disease (fewer than 5 metastatic lesions) amenable to standard therapy will be excluded.
11. Major surgery within 4 weeks or minor surgery or biopsy within 1 week of the first dose administration.
12. Patients who have had RT to the region of the rectum or will require RT to the region of the rectum during the trial.

    NOTE: Metastatic castration-resistant prostate cancer [mCRPC] patients who have received prior prostate or prostate fossa radiation and radiation to nearby lymph nodes, where the rectum is not the target, can be included in this study.

**Prior/Concomitant Therapy**

13. Uncontrolled active infection requiring intravenous antibiotic, antiviral or anti-fungal medications within 14 days before the first dose administration. Infections (e.g., urinary tract infection) controlled on concurrent anti-microbial agents and anti-microbial prophylaxis per institutional guidelines are acceptable.
14. Receiving or having received anticancer treatment within the following period prior to the first dose administration:
    - Cytotoxic treatment: 3 weeks.
    - Non-cytotoxic drugs, including small molecule investigational products: 3 weeks or 5 terminal half-lives from plasma (whichever is the longest).
    - Biological products including investigational immune-oncology agents: 4 weeks.
    - Radiation with a limited field for palliation: 4 weeks.
    - Radiation to > 30% of the bone marrow: 4 weeks.
    - Lung radiation: 60 days.
15. Patient has received corticosteroids at a dose of > 10 mg prednisone/day or equivalent for any reason within 4 weeks prior to receiving the first dose administration.
16. History of hypersensitivity to active or inactive excipients of study drug or drugs with a similar chemical structure or class to the study drug.

**Other Exclusions**

17. Patient is not willing to use suppositories.
18. Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.
19. Patient has a positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 prior to Screening or enrollment, or has clinical signs and symptoms consistent with SARS-CoV-2 infection; e.g., fever, dry cough, dyspnea, sore throat, fatigue or positive SARS-CoV-2 test result within 2 weeks prior to Screening. Patients who had symptomatic COVID-19 disease less than 1 month prior to Screening will be excluded. If a patient has had a severe course of COVID-19 (extracorporeal membrane oxygenation, mechanically ventilated) within 4 weeks of Screening, or have any sequelae of infection or ongoing infection, the patient will also be excluded. If the patient has had recent (within previous 14 days) exposure to someone who has COVID-19 symptoms, been in contact with someone

who has tested positive for COVID-19 or visited a COVID-19 treatment facility, the patient may be re-evaluated for participation in the study after undergoing an isolation period of at least 10 days and having a negative SARS-CoV-2 RT-PCR test prior to enrollment.

## 5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (e.g., eligibility requirements failed), and any SAEs will be recorded in the electronic case report form (eCRF).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. This will be assessed on a case-by-case basis and requires Sponsor and Clinical Research organization (CRO)'s prior approval before the patient is rescreened. Rescreened patients should be assigned a different unique participant number from the initial screening. The previous screening number will be noted separately for reference purposes.

### 5.3.1 Screening and Enrollment Log and Participant Identification Numbers

The patient's enrollment will be recorded in the Screening and Enrollment Log.

Upon screening, each patient will receive a unique participant identification number. Participant numbers must not be re-used for different patients.

# 6 Study Drug

Study drug is defined as any investigational drug(s) (including marketed product[s]) intended to be administered to a study participant according to the study protocol.

On days when study drug and EBRT are to be administered, it is advised that NOX66 is given at least 1 hour prior to EBRT.

## 6.1 Study Drug(s) Administered

Details on study drug administered during this study are given in Table 6-1.

**Table 6-1 Study Drug(s) Administered**

| | Part 1 | | | | Part 2 | |
|---|---|---|---|---|---|---|
| **Dose Cohort/ Arm:** | **Dose Cohort 1** | **Dose Cohort 2** | **Dose Cohort 3** | **Dose Cohort 4** | **Arm 1** | **Arm 2** |

| **Drug Name:** | NOX66 800 mg | NOX66 1200 mg | NOX66 1600 mg | NOX66 2400 mg | RP2D | RP2D |
|---|---|---|---|---|---|---|
| **Type:** | Small molecule | | | | | |
| **Dosage Formulation:** | Suppository containing idronoxil in a lipophilic base | | | | | |
| **Unit Dose Strength(s):** | 400 mg or 600 mg | | | | | |
| **Dosage Level(s):** | 1 x 400 mg suppository administered twice daily. Total daily dose of 800 mg. | 1 x 600 mg suppository administered twice daily. Total daily dose of 1200 mg. | 2 x 400 mg suppository administered twice daily. Total daily dose of 1600 mg. | 2 x 600 mg suppository administered twice daily. Total daily dose of 2400 mg. | To be determined | To be determined |
| **Route of Administration:** | Rectal | | | | | |
| **Use:** | Interventional | | | | | |
| **IMP and NIMP:** | IMP | | | | | |
| **Sourcing:** | Provided centrally by the Sponsor. | | | | | |
| **Dosing Instructions:** | Twice daily NOX66 dosing should occur at least 10 hours apart. Where 2 suppositories are administered per dosing, each suppository will be administered at least 5 minutes apart. The same administration schedule should be adhered to on the days when EBRT is administered. Patients or care givers should always wear gloves when handling and/or during administration of NOX66. The use of a small amount of water-soluble lubricant is advised before rectal administration. No oil- or wax-based lubricants should be used during rectal administration. Patients will be provided with an "Instructions for Administration of NOX66 Suppositories" that contains further details. | | | | | |
| **Packaging and Labeling:** | Each suppository is supplied in individually sealed PVC suppository packaging shells and boxed in appropriate quantities for the clinical study. Each box will be labeled as required per country requirement. | | | | | |

IMP = investigational medicinal product; RP2D = recommended Phase 2 dose

From Cycle 3 onwards, study drug for 2 cycles will be dispensed every second cycle (i.e., Cycles 5, 7, 9, 11 etc.). From Cycle 5 onwards, on-site visits will occur on a 28-day (4 weekly) basis, i.e., patients will visit the clinical unit every second cycle. After Cycle 5, the next patient visit will therefore be Cycle 7, followed by Cycle 9, etc. until the patient completes the treatment period or is withdrawn.

In patients who have regular bowel movements (i.e., within several hours after waking), patients will be instructed to insert the suppository after the bowel movement. To promote regular bowel movements, patients should be encouraged to consume a high fiber diet, with adequate amounts of water. In those patients who are not on a regular bowel movement schedule, insertion of the

suppository should occur at regularly scheduled times individualized for the patient (but approximately 10 hours apart).

For Days 1, 2, 6 and 14 of Cycle 1 and Day 1 of Cycles 2 and 3 (PK days), once the suppository is inserted in the rectum and defecation occurs within 2 hours after the administration, the remaining doses should be administered at the prescribed time as scheduled. No re-dosing is permitted if defecation occurs within 2 hours of administration.

The dosing time for suppository/ies administration must be recorded by the patient in the Patient Study Drug Administration Diary which must be brought to the study center at each on-site visit.

### 6.1.1 Radiotherapy

The choice of dose/fraction as stated below is Investigator's discretion based on patient's need. Sites will need to follow institutional practice and the guidance provided in Appendix 10 (Section 10.10) for low-dose EBRT administration.

The study population consist of patients with mCRPC, BC, NSCLC or other solid tumors who have failed at least one line of prior treatment and for whom, according to the Investigator, are eligible for low-dose EBRT for at least one symptomatic or minimally symptomatic lesion (for the prevention of symptoms).

The dose levels of EBRT will be either:

- 8 Gy as a single fraction, or
- 20/25 Gy as 5 fractions given over 5 to 10 days.

The first EBRT dose fraction must be on Day 2 of Cycle 1 and the remaining dose fractions will be given between Day 3 and Day 11. The choice of one of the EBRT dose/fractions as stated above will be at the discretion of the Investigator and will be determined by the clinical requirements of the patient. A maximum of 2 sites can be irradiated concurrently in conjunction with NOX66 during Cycle 1. EBRT will be administered according to the institutional protocol.

Additional EBRT at the dose levels/fractions stated above may be given during the study. However, should additional EBRT be considered necessary during the study (Cycle 2 onwards), the Investigator should communicate this to the Medical Monitor for team acknowledgment since extra doses could impact study results.

## 6.2 Preparation, Handling, Storage, and Accountability

The Investigator or designee must maintain a log to confirm appropriate temperature conditions (2°C to 8°C [35.6°F to 46.4°F], away from direct light) have been maintained during transit for

all study drug received and any discrepancies are reported and resolved before use of the study drug.

Patients must be advised that during travel from the study center to their homes the study drug must be stored at 2°C to 8°C (35.6°F to 46.4°F), away from direct light, and they should avoid leaving the study drug in their vehicle on a hot day. They should also not keep the study drug on their person as the study drug will melt at body temperature. At home the study drug should be stored in the fridge and handled as little as possible upon administration to prevent melting. Further details are provided in the "Instructions for Administration of NOX66 Suppositories".

Only patients enrolled in the study will receive study drug and only authorized site staff will supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator or designated staff (where applicable) is responsible for study drug accountability, reconciliation and record maintenance (e.g., receipt, reconciliation and final disposition records).

Further guidance and information are provided in the "Instructions for Administration of NOX66 Suppositories" document that will be provided by the Sponsor to patients and study staff.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Each site must submit a completed Participant Enrollment Form to the Sponsor or CRO designee for approval to patient in the study. The Sponsor's representative (Parexel) will review the information to verify that the patient meets all inclusion criteria and none of the exclusion criteria to determine if the patient is eligible for study participation. The Investigator must not prescribe or administer the study drug until the patient has completed registration and has been approved to participate in the study.

No randomization will be done for Parts 1 and 2 as patients will all receive NOX66 and EBRT treatment. Therefore, patients will be enrolled sequentially in dose cohorts of Part 1 and in parallel for Part 2.

The clinical site will be assigned a unique 4-digit number and each patient will be assigned a unique screening number after written informed consent is obtained. Each patient will have a unique identifier (6-digit number [XXXX-YY]) that combines both the site (XXXX) and screening number (YY). Participant numbers will be assigned sequentially at the clinical site.

## 6.4 Study Drug Compliance

NOX66 is packaged with each suppository individually sealed in plastic packaging and boxed as quantities to meet the treatment needs. The study drug is to be stored refrigerated (2°C to 8°C [35.6°F to 46.4°F]).

The suppository units are packed in individually sealed PVC suppository packaging shells and boxed in appropriate quantities. Label information for the primary packaging will include, but are not limited to the study number, name of the product, lot number, route of administration and Sponsor name.

Label information for the secondary package box which contains the suppository units will include but are not limited to the Sponsor's name and address, study number, name of the product, lot number, re-assay date, storage conditions, dosage and patient identifier.

All dosages of NOX66 will be self-administered by the study patients or administered by a caregiver. A missed dose should be taken as soon as it is noted if it has not been longer than 2 hours. If the period exceeds 2 hours, the missed dose should be skipped.

When patients are dosed at the site (Days 1, 2, 6 and 14 of Cycle 1 and Day 1 of Cycles 2 and 3), they must bring the study drug received at the start of the treatment cycle to the study site and will administer the study drug under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents, eCRF and Patient Study Drug Administration Diary for treatment compliance. The dose of study drug and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

When NOX66 is self-administered by the patients or administered by their care giver at home (all dosing days except the mornings of Days 1, 2, 6 and 14 of Cycle 1 and Day 1 of Cycles 2 and 3), compliance with study drug will be assessed at each visit. The patient or care giver should use gloves for drug administration. Compliance will be assessed by direct questioning and counting returned unused suppositories during the site visits and documented in the source documents and eCRF. Patients will also receive a Patient Study Drug Administration Diary in which they must record details of each dosing (e.g., date and time of dosing, number of suppositories, missed doses). Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of NOX66 suppositories dispensed to and taken by each patient must be maintained and reconciled with study drug and compliance records for each cycle. Actual drug

start and stop dates, including dates for drug delays and/or dose reductions will also be recorded in the eCRF.

## 6.5 Concomitant Therapy

Any medication (e.g., ADT [for mCRPC patients], bisphosphonates or denosumab, pain medication) or vaccine (including COVID-19 vaccine, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor. Please see Sections 8.2.2.4.1 and 8.2.2.4.2, respectively, for details on permitted and prohibited medications.

## 6.6 Dose Modification

In patients who develop significant toxicity determined to be related to NOX66 after Cycle 1, the Investigator may reduce the number of suppositories or the daily dose for the patient to remain in the study (Table 6-2).

In the first occurrence of any AE > Grade 1 due to NOX66 (excluding Grades 1 and 2 anal/perianal rash), NOX66 treatment will be put on hold until the AE resolves to Grade 1 after which dosing can be restarted with the same dose level. If the AE occurs again, NOX66 treatment should be put on hold until the AE resolves to Grade 1 after which dosing may be restarted with a lower dose, i.e., reduced number of suppositories (Table 6-3). Grades 1 and 2 anal/perianal rash should be managed with hydrocortisone cream; no treatment hold is required in these cases.

**Table 6-2 Dose Modification of Study Treatment NOX66**

| Current Dose | | Dose Reduction | |
|---|---|---|---|
| **Total Daily Dose** | **Number of Suppositories/Day** | **Total Daily Dose** | **Number of Suppositories/Day** |
| 800 mg (400 mg BID) | 2 | 400 mg (once daily) | 1* |
| 1200 mg (600 mg BID) | 2 | 600 mg (once daily) | 1* |
| 1600 mg (800 mg BID [2× 400 mg per administration]) | 4 | 800 mg (400 mg BID) | 2 |
| 2400 mg (1200 mg BID [2 × 600 mg per administration]) | 4 | 1200 mg (600 mg BID) | 2 |

BID = twice daily

* To be administered during evening dosing.

**Table 6-3 Management of NOX66 Treatment-related Toxicity**

| Event (NCI-CTCAE v5.0) | Action |
|---|---|
| Grades 1 to 2 toxicity (all events) | Investigator judgement to continue treatment or interrupt dose (maximum 28 days), except for Day 1 of a new cycle of study treatment, as described above. Initiate optimal supportive care and causality investigation. Consider resuming at the same dose level when toxicity has resolved or is resolving with prophylactic treatment (if appropriate). If toxicity recurs on rechallenge and does not resolve in < 7 days despite optimal supportive care, consider a dose reduction. |
| Grade 3 to 4 toxicity (1st event) | Interrupt study treatment and initiate optimal supportive care and causality investigation. Maximum treatment interruption is 28 days. When toxicity has resolved or is resolving with prophylactic treatment (Grade ≤ 2 or returns to baseline), consider restarting NOX66 with reduced number of suppositories per day and prophylactic treatment (if appropriate). |
| Grade 3 toxicity (recurrence of the same AE) | Interrupt study treatment and initiate optimal supportive case and causality investigation. Maximum treatment interruption is 28 days. When toxicity has resolved or is resolving (Grade ≤1 or returns to baseline), consider restarting NOX66 with reduced number of suppositories per day and prophylactic treatment (if appropriate). After 2 dose reductions, consider permanent discontinuation of NOX66 for Grade 3 events. |
| Grade 4 toxicity (recurrence of the same AE) | Patients should permanently discontinue NOX66 treatment. |

AE = adverse event; NCI-CTCAE = national cancer Institute-Common Terminology Criteria for Adverse Events

If a perineal and/or anal rash develops (Grade 1 to 2), a topical hydrocortisone containing hemorrhoid cream/ointment and/or cutaneous cream should be used. For Grade 3 to 4 perineal and/or anal rash, NOX66 treatment should be delayed until the rash has resolved to Grade 1 or completely and hydrocortisone cream should be used as appropriate. NOX66 should also be

delayed if there is proctitis, rectal mucositis or an ulcer of Grade 2 or higher. Treatment may be resumed when toxicity has decreased to Grade 1. Treatment with NOX66 should also be delayed in the presence of anorectal infections and may be resumed after they are resolved. See also Section 7.1.1 for details on handling of dose delays.

### 6.6.1 Dose Modification of Radiotherapy

The Investigator may adjust the dose of radiotherapy based on the standard operating procedure (SOP) of the site if the patient experiences intolerance or severe toxicity to radiotherapy during the study period.

Patients who are eligible for an additional course of radiotherapy to the same or other lesion due to chronic pain or new symptomatic lesion (not related to progression) may receive an additional course of EBRT (8 Gy or 20/25 Gy given as 1 or 5 fractionated doses, respectively). If such a case occurs, it should be discussed with the Medical Monitor before administration of the additional course.

## 6.7 Study Drug After the End of the Study

All patients will receive NOX66 treatment from Cycle 1 until disease progression, unacceptable toxicity, withdrawal of consent, start of a new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by Sponsor. The entire study will finish when the last patient enrolled in Part 2 completes 6 months treatment. All patients receiving study drug at that time will be switched to the NOX66 compassionate access program. Those patients on the compassionate access program will continue to receive NOX66 treatment until disease progression or unacceptable toxicity. These patients will be followed until death, or the patient is lost to follow-up.

# 7 Discontinuation of Study Drug and Participant Discontinuation

## 7.1 Discontinuation of Study Drug

### 7.1.1 Safety Stopping Criteria:

It may be necessary for a patient to permanently discontinue (definitive discontinuation) study drug. If study drug is definitively discontinued, the patient will remain in the study to be evaluated for clinical observation and safety monitoring. See the SoA (Table 1-1 [Parts 1 and 2]) for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

Patients may be discontinued from study drug in the following situations:

- Patient decision. The patient free to discontinue study drug at any time, without prejudice to further treatment.
- Any AE that in the opinion of the Investigator or Sponsor contraindicates dosing or meets the criteria for discontinuation.
- Recurrence of the same Grade 3 AE, even if recurrence is at a lower dose of study drug, with the exemption of localized skin reactions associated with drug administration which responds to topical corticosteroids.
- Unacceptable toxicity.
- Severe noncompliance with the protocol.
- Disease progression or unacceptable toxicity.
- Patient started alternative anticancer therapy including another investigational agent.
- Patient is lost to follow-up.

For patients with mCRPC, study drug will not be stopped due to rises in PSA alone. The Prostate Cancer Working Group 3 (PCWG-3) emphasized the importance of keeping patients on the study until radiographic or symptomatic progression, which better reflects the clinical course.

#### 7.1.1.1 Temporary Discontinuation

Study drug administration may be stopped temporarily (up to 21 days) due to AE(s) and will be restarted after the AE resolves to Grade 1. If an AE has not resolved after this period, but the Investigator confirms there is clinical benefit for the patient to continue study participation, this period could be extended upon discussion with Medical Monitor and Sponsor. If the AE still has not resolved after this extended period, and no clinical benefit was confirmed then the patient will be discontinued from study drug.

### 7.1.2 Dose Escalation Rules and Safety Steering Committee

A dose in which the safety stopping criteria have been met (Section 7.1.1) or where toxicity was observed based on the DLT assessment criteria (Section 7.1.2.2) will not be repeated and further dose escalation will not occur. Where stopping criteria have not been met, the decision of the SSC may be to give the next intended dose, a smaller than the predefined dose increment, a repeated dose or to stop dosing. There will be a temporary halt for enrollment after the first 3 patients are enrolled in each cohort until the SSC clears that the dose level is safe to continue the dose escalation.

Measures to ensure data integrity and safety of patients will be detailed in the Data and Safety Monitoring Plan.

If the Investigator, the Medical Monitor or the Sponsor becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding.

Should the study be terminated, and/or the study center closed for whatever reason, all documentation pertaining to the study and study drug must be returned to Sponsor. Any actions of the study site required for assessing or maintaining patient safety will continue as required, despite termination of the study by the Sponsor.

#### 7.1.2.1 Safety Steering Committee

The safety of the patients enrolled in this study will be closely monitored on an ongoing basis by an SSC during dose escalation review meetings. The SSC will review clinical data from the study, including safety, available efficacy and PK data (if available), and will ensure the appropriate selection of doses to be used in the dose escalation and dose expansion phases of the study. All safety data collected up to Cycle 1 Day 21 for each patient will be reviewed.

The SSC will consist of:

- The Sponsor's Study Team Physician or a designee.
- Clinical Research Organization's Medical Monitor, who will chair the committee.
- The Investigators or a designee from every participating site, at least from sites which enroll patients in the respective dose cohort.
- Other Sponsor and Parexel team members.

The SSC charter will define the exact membership and who should be present for recommendations to be made.

For the initiation of a new dose level, the SSC will evaluate the available safety, tolerability and PK data (if available) of NOX66 in combination with EBRT. Once 3 patients have completed their DLT assessment period, the SSC will review and assess all available safety data to make recommendations regarding that dose and/or the next dose/study part. The decisions and decision-making regarding the next dose level will be documented and provided to the Investigators prior to dosing of new patients. The final decision regarding dose escalation or dose de-escalation will be made by the SSC.

The SSC will be responsible for the following:

- Assessment of all available safety, tolerability and exposure data during the study.
- Defining patients who have experienced a DLT per protocol definitions of DLT (see Section 7.1.2.2).
- All recommendations regarding dose escalation or dose de-escalation of NOX66. The SSC may recommend proceeding with dose escalation, expand the current dose level with additional patient enrollment or de-escalate the dose to a lower dose level.
- All recommendations regarding modification of NOX66 dosing schedule, if required. The SSC may recommend adjusting the NOX66 dose, dosing frequency or schedule during either Cycle 1 or subsequent cycles. In this situation, the protocol must be amended.
- All recommendations relating to initiation of Part 2 enrollment.
- Recommendation for cessation of dose escalation.
- The review of safety and tolerability of both doses of EBRT (8 Gy and 20/25 Gy administered as 1 or 5 fractionated doses).
- All recommendations regarding the replacement of any excluded or withdrawn patients on study, if necessary.*

* Any patient initiated on treatment in error (i.e., because he or she failed to meet inclusion and/or exclusion criteria) but meeting the criteria of an evaluable patient, will be reviewed on a case-by-case basis by the SSC to determine if the patient should be included or excluded in the recommendation for dose escalation.

See Section 7.1.2.2 for details on DLT assessment.

### 7.1.2.2 Assessment of Dose-limiting Toxicities

A DLT is defined as an AE that occurs during Cycle 1 (Day 1 to Day 21) that is assessed as unrelated to the disease, intercurrent illness or concomitant medications and that, despite optimal therapeutic interventions, meets any of the following criteria (judged to be associated with NOX66 alone or in combination with EBRT [possibly, probably or definitely related to]):

1. Grade 3 or higher non-hematological toxicities (excluding alopecia) with the following exceptions:
    a. Grade 3 nausea/vomiting or diarrhea < 72 hours with adequate antiemetic and other supportive care

b. Grade 3 fatigue < 1 week

c. Grade 3 or higher electrolyte abnormality that lasts 24 to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical drugs

2. Grade 4 non-hematologic (non-laboratory) toxicity of any duration.
3. Grade 3 or Grade 4 febrile neutropenia of any duration.
4. Grade 4 neutropenia or thrombocytopenia > 5 days.
5. Grade 3 thrombocytopenia with bleeding.
6. Grade 3 thrombocytopenia in combination with a Grade 3 or greater blood and lymphatic system disorder.
7. Grade 3 AST or ALT that is associated with a Grade 2 or greater rise in bilirubin that lasted for more than 7 days.
8. Any AST or ALT > 8 × ULN regardless of duration (5 to 8 × ULN for up to 2 weeks is allowed).
9. Any AE that results in a treatment delay or hold of > 14 days.

Grading of DLTs will follow the guidelines provided by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

All AEs of the grades specified above count as DLTs unless they are clearly and incontrovertibly due to disease progression or extraneous causes.

After all patients enrolled in a cohort complete Cycle 1, and the data from these patients are available, a dose escalation meeting will be conducted. At least 3 evaluable patients are required in order to proceed with DLT evaluation for each cohort.

The criteria for determination of an evaluable patient for a dose escalation decision or determination of the MTD, must include:

- Patient who experienced a DLT during the 21-day treatment cycle (Cycle 1), or
- Patient who has not experienced a DLT and has taken at least 80% of the prescribed daily doses of NOX66 and completed all safety evaluations.

For each dose escalation cohort, additional patients may be enrolled or replaced if a patient discontinues prior to the completion of Cycle 1 for reasons other than safety. Patients who develop a DLT and discontinue treatment will not be replaced.

If a patient develops any DLT during Cycles 2 to 6, these will be considered 'DLT equivalent toxicity' and will be recorded in the eCRF. This information may be considered during SSC review to assess dose escalation.

When a DLT occurs, the site must immediately inform Parexel who will then inform the other sites that a DLT has occurred and evaluate if a second DLT has occurred at any other sites.

Assessment of toxicities and decisions about dose recommendation for Part 1 (dose escalation) will be made during the SSC meeting.

## 7.2 Participant Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or administrative reasons. The patient will be definitively discontinued from both the study drug and from the study at that time.

The primary reason for a patient withdrawing prematurely should be recorded in the patient's source records and on the eCRF. In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Investigator to keep the patient in the study. Patients who discontinue study drug because of an AE but agree to participate with any follow-up assessments will undergo the EOT/ED Visit and will be requested to return for the Follow-up Visits. The Investigator must contact the Medical Monitor promptly when deciding if a patient should be withdrawn or if the patient elects to stop the study.

Patients withdrawn from this study cannot re-enroll. Patients who discontinue for a non-safety related reason may be replaced if the patient is withdrawn during Cycle 1 in Part 1. Withdrawal of consent must be ascertained and documented by the Principal Investigator who must consult with the Medical Monitor and document the withdrawal of consent in the eCRF and in the medical records. Patients will be asked about the reason(s) for withdrawal and the presence of any AEs. Should the patient agree to be followed for safety information, this should be documented in the medical records.

Patients experiencing adverse reactions should be followed until the AE has resolved, stabilized or is no longer deemed clinically significant, as judged by the Investigator. Appropriate supportive and/or definitive therapy will be administered as required.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he or she may request destruction of any samples taken and not tested and the Investigator must document this in the site study records.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. Refer to the SoA (Table 1-1 [Parts 1 and 2]) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

## 7.3 Loss of Participants to Follow-Up

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

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record/eCRF.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

# 8 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Table 1-1 [Parts 1 and 2]). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study drug.

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

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

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

Repeat or unscheduled samples may be taken for safety reasons.

## 8.1 Efficacy Assessments

Efficacy will be assessed by evaluating the change from baseline PSA for patients with mCRPC (Section 8.1.1). For all patients, DCR (as measured by complete response [CR], PR and SD; Section 8.1.2) will also be evaluated based on change from baseline imaging using RECIST v1.1 criteria. In mCRPC patients, bone lesions will be evaluated using PCWG-3 criteria (Section 8.1.3). Other assessments to be performed during this study are ECOG scores, pain severity (Section 8.1.4), morphine and analgesic use (Section 8.1.6) and change from baseline Patient Reported Outcomes (PROs) using the questionnaires listed in Section 8.1.5 for all patients enrolled in the study.

Efficacy will also be assessed by looking at the skeletal-related events (SREs) and symptomatic skeletal events (SSEs) (Section 8.1.7), progression-free survival (PFS; Section 8.1.8), overall survival (OS; Section 8.1.9), and overall or objective response rate (ORR; Section 8.1.10).

### 8.1.1 Prostate-specific Antigen (PSA) Response and Progression (mCRPC only)

Blood for PSA assessment will be collected during Screening, on Day 1 of Cycles 1 to 5, every second cycle thereafter (i.e., Cycles 7, 9, 11 etc.), at the EOT/ED Visit and at the 6-, 9- and 12-month Follow-up Visits for all patients including those who discontinue the study for any reason other than disease progression (Table 1-1 [Parts 1 and 2]). Patients who discontinue the study drug for reasons other than disease progression will continue to have PSA evaluated until disease progression, withdrawal of consent, initiation of new anticancer therapy, the end of the 12-month follow-up period or death, whichever comes first. Patients who discontinue the study

drug due to disease progression do not need to provide PSA samples during the Follow-up Visits. PSA will be used as a blood-based biomarker for tracking and monitoring the response state during the study for mCRPC.

A PSA response will be considered as a PSA value reduction ≥ 30% from baseline at the end of Cycles 3 and 6. A PSA response reduction from baseline at any time point will also be assessed as a secondary objective.

According to PCWG-3, a sequence of rising PSA values should be obtained at a minimum of 1-week intervals with a starting value of 2.0 ng/mL. PSA PFS is the time from first dose administration to PSA progression or death.

### 8.1.2 Disease Control Rate

Disease control rate is measured by the percentage of patients with a best overall confirmed response of CR or PR at any time plus SD from first dose administration until disease progression or death due to any cause or the start of new anticancer therapy. CR, PR plus SD will be assessed based on RECIST v1.1 (Table 1-1 [Parts 1 and 2]).

### 8.1.3 Tumor Imaging Assessment

In this study, the preferred assessment of soft tissue lesions is CT or MRI scans using RECIST v1.1 criteria and the preferred assessment method for bone lesions is bone scan using PCWG-3.

Tumor imaging using RECIST v1.1 and PCWG-3 criteria will be performed during within 28 days prior to enrollment, every 8 weeks (± 7 days) from the first study dose administration up to Week 26, and every 12 weeks (± 7 days) thereafter until disease progression (as defined by RECIST v1.1 and PCWG-3 criteria), withdrawal of consent, initiation of new anticancer therapy or death. Tumor imaging should ideally be performed during the rest period before the start of the next treatment cycle.

- If a patient permanently discontinues the study drug due to disease progression according to RECIST v1.1 criteria, a tumor imaging and disease response assessment is not required.
- If a patient permanently discontinues the study drug due to clinical disease progression, a tumor imaging and disease response assessment does not need to be repeated if completed ≤ 28 days after the last dose of study drug.

For patients who permanently discontinue study drug for any reason other than confirmed disease progression, tumor imaging and disease response assessments will continue to be

performed every 12 weeks (± 7 days) for up to 12 months after the last dose of the study drug until disease progression, withdrawal of consent, initiation of new anticancer therapy, the patient is lost to follow-up or death, whichever comes first.

- If a patient meets disease progression during the follow-up period according to RECIST v1.1 criteria, a tumor imaging and disease response assessment is not required.
- If a patient meets clinical disease progression during the follow-up period, a tumor imaging and disease response assessment does not need to be repeated if completed ≤ 28 days after the date of clinical disease progression.

For patients who permanently discontinue the study drug or the follow-up period due to withdrawal of consent, the Investigator is to obtain tumor imaging and conduct a disease assessment at the time of the ED Visit or final Follow-up Visit if the patient agrees. A tumor imaging and disease response assessment does not need to be repeated if completed ≤ 28 days of the date of withdrawal of consent.

The same imaging method should be used for a patient throughout the study and images should be read on site. In Part 2 of the study, images should read on site and also be submitted in digital format to a Central Imaging Provider as detailed in the Investigator Site Operations Manual.

Baseline scans shall be assessed and any lesions which can be measured in accordance with RECIST v1.1 or PCWG-3 (CT or MRI) criteria will be noted as “target lesions”. Target measurable lesions may either be at the site of irradiation or non-irradiation and the number of lesions will be capped at 10 lesions (for RECIST v1.1). Patients with identified measurable target lesions will be assessed for overall response using RECIST v1.1 criteria. In addition to RECIST v1.1, all measurable lesions (irradiated and non-irradiated) will be measured and monitored for change (including new lesions). To identify abscopal responses, all lesions will be evaluated.

At a minimum, imaging of the chest, abdomen and pelvis should be performed using consistent imaging modality (CT or MRI). Any other areas of disease involvement should be additionally investigated based on the signs and symptoms of individual patients. During the assessments, subsequent to baseline, any other sites at which new disease is suspected should also be appropriately imaged.

Bone scans will be used for qualitative evaluation of lesions and quantitative evaluation of new and/or resolved lesions. Bone scans will be assessed using PCWG-3 criteria.

The RECIST v1.1 and PCWG-3 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumor response criteria are presented in Section 10.5.

### 8.1.4 Eastern Cooperative Oncology Group Performance Status Score

Eastern Cooperative Oncology Group Performance Status Score[5] will be evaluated by the Investigator at Screening, Day 1 of Cycles 1 to 3, every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.) and the EOT/ED Visit (Table 1-1 [Parts 1 and 2]). The assessment should be performed by the same Investigator throughout the study, whenever possible.

**Table 8-1 Eastern Cooperative Oncology Group Performance Status Score**

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

### 8.1.5 Clinical Outcome Assessment

A Clinical Outcome Assessment is any assessment that may be influenced by human choices, judgement or motivation and may support either direct or indirect evidence of treatment benefit. Patient reported outcome is one of these types of Clinical Outcome Assessments.

Patient reported outcome, an umbrella term referring to all outcomes and symptoms, are directly reported by the patient. Patient reported outcomes have become a significant endpoint when evaluating effectiveness of treatments in clinical trials.

Questionnaires are to be completed before any other study assessments performed on the day of the visit.

The following PRO instruments will be administered for analysis of the PRO endpoints in this study:

- **European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients (EORTC-QLQ-C30)**
  The EORTC-QLQ-C30 is a well-established PRO questionnaire developed to monitor health-related Quality of Life (QoL) outcomes among cancer patients (Section 10.6). The questionnaire assesses important functioning domains (e.g., physical, emotional, social) and common cancer symptoms (e.g., fatigue, pain, nausea, vomiting, appetite loss). The questionnaire will be completed at Screening, on Day 1 of Cycles 3 and 5, followed by every 4 cycles thereafter (e.g., Cycle 9, Cycle 13 etc.), and at the EOT/ED Visit (Table 1-1 [Parts 1 and 2]).
- **Brief Pain Inventory – Short Form (BPI-SF)**
  Worst pain, general pain and pain's interference with daily life will be assessed during the study drug using the BPI-SF (Section 10.7). The questionnaire will be completed at Screening, on Day 1 of Cycles 3 and 5, followed by every 4 cycles thereafter (e.g., Cycle 9, Cycle 13 etc.), and at the EOT/ED Visit (Table 1-1 [Parts 1 and 2]). The BPI-SF comprises a total of 15 items measuring 2 domains: pain severity and pain interference. Items measuring pain severity (including 'worst pain') are rated on an 11-point numeric rating scale ranging from 0=No pain to 10=Pain as bad as you can imagine. All BPI-SF items are measured using a 24-hour recall period.
- **Functional Assessment of Cancer Therapy – Prostate (FACT-P)**

  The FACT-P questionnaire is a relevant, worldwide tool used for assessing the health-related QoL in men with prostate cancer. The FACT-P is a 39-item questionnaire composed of the FACT-General (FACT-G) original subscales (Physical Well-being, Social/Family Well-being, Emotional Well-being and Functional Well-being) and a Prostate Cancer Subscale (Section 10.9). Each item is rated on a 5-point scale ranging from 0 (not at all) to 4 (very much). A higher score indicates a better QoL. The questionnaire will be completed by mCRPC patients only at Screening, on Day 1 of Cycles 3 and 5, followed by every 4 cycles thereafter (e.g., Cycle 9, Cycle 13 etc.), and at the EOT/ED Visit (Table 1-1 [Parts 1 and 2]).
- **Patient Experience Questionnaire (PEQ)**

  The Sponsor has developed a questionnaire to evaluate the patient's experience with the suppository dosage form (Section 10.8).

  The PEQ will be completed on Day 2 of Cycle 1, Day 1 of Cycle 3 and at the EOT/ED Visit (Table 1-1 [Parts 1 and 2]).

### 8.1.6 Morphine Administration and Analgesic Use

The dose and frequency of morphine administration and analgesic use will be assessed at each on-site study visit based on the patient's concomitant medication use assessment.

### 8.1.7 Skeletal-related Events and Symptomatic Skeletal Events Assessment

Skeletal-related events and SSEs will be evaluated based on the patient's clinical history and examinations, including but not limited to incidence of fractures and pain. Assessments will be performed at each on-site study visit.

### 8.1.8 Progression-free Survival

Progression-free survival is defined as the duration of time from first dose administration to date of disease progression is objectively documented, including tumor progression, early discontinuation or death prior to data cut-off. Patients alive and progression-free at the time of data cut-off will be censored at the date last known alive. Progression-free survival will be assessed every 8 weeks (± 7 days) from the first dose administration up to Week 26, and every 12 weeks (± 7 days) thereafter until disease progression according to RECIST v1.1 criteria.

### 8.1.9 Overall Survival

Overall survival is defined as time from the date of first dose administration to date of death due to any cause. Patients alive at the time of data cut-off will be censored at date last known alive.

### 8.1.10 Overall or Objective Response Rate

Response rate is defined as the proportion of patients who have confirmed CR or PR by objective disease progression RECIST v1.1, as assessed by the Investigator/local radiologist. Overall or ORR will be assessed every 8 weeks (± 7 days) from the first dose administration up to Week 26, and every 12 weeks (± 7 days) thereafter until disease progression.

Complete response is defined when all target lesions present at baseline have disappeared (with the exception of lymph nodes which must be < 10 mm to be considered nonpathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the target lesions has decreased by 30% or more compared to baseline (with no evidence of progression).

## 8.2 Safety Assessments

### 8.2.1 Administrative Procedures

#### 8.2.1.1 Informed Consent

Informed consent must be documented according to Section 10.1.3.

#### 8.2.1.2 Participant Identification Card

All patients will be given a patient identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the patient with a patient identification card immediately after the patient provides written informed consent.

The patient identification card also contains contact information so that a healthcare provider can obtain information about study drug in emergency situations where the Investigator is not available. At the time of enrollment/study drug allocation, site personnel will add the study drug dosage to the patient identification card.

### 8.2.2 Screening and Eligibility Assessments

#### 8.2.2.1 Eligibility Criteria

All inclusion and exclusion criteria (Section 5.1 and Section 5.2) will be reviewed by the Investigator or designee to ensure that the patient qualifies for the study. Review of eligibility criteria will be done at Screening and at the Day -1 visit.

#### 8.2.2.2 Participant Demographics and Baseline Characteristics

Demographic data will be collected including age (at the day of Screening), gender, race, ethnicity and baseline characteristics (e.g., tobacco and smoking history, alcohol consumption history) as allowed by the local regulations.

#### 8.2.2.3 Medical History

A medical history will be obtained by the Investigator or qualified designee at Screening. The medical history will collect all active and chronic conditions from each patient. Gleason score will be collected as part of the medical history for patients with mCRPC only. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not

listed as medical history. If the patient has data available from any historical genetic assays conducted to identify genetic variations, this will also be collected (all patients).

#### 8.2.2.4 Prior and Concomitant Medications Review

The Investigator or qualified designee will review prior medication use and record prior medications taken by the patient within 30 days prior to the Screening Visit.

The Investigator or qualified designee will record medication, if any, taken by the patient during the study through the last visit. Concomitant medications will be recorded for 30 days after the last dose of study drug (or longer if related to an SAE).

##### 8.2.2.4.1 Permitted Medications

Analgesic agents, ADT, bisphosphonates and denosumab are allowed to be used during the study. The Investigator or qualified designee will review the use of analgesic agents taken by the patient as part of the concomitant medications review (see SoA [Table 1-1 (Parts 1 and 2)]).

Anti-microbial agents to control infections (e.g., urinary tract infection) are allowed as per SOC guidelines.

Topical hydrocortisone-containing hemorrhoid cream/ointment and/or cutaneous cream is allowed for the treatment of a perineal and/or anal rash and can be administered straight after study drug administration, and as frequently as required as per institution.

The use of a small amount of water-soluble lubricant is advised before rectal administration. No oil- or wax-based lubricants should be used during rectal administration.

##### 8.2.2.4.2 Prohibited Medication

The following medications and therapies are not allowed during the study:

- Any concomitant chemotherapy.
- Oral or parenteral glucocorticoids and herbs known to alter PSA levels.
- Other investigational agents.
- Inducers (phenobarbital) and inhibitors (valproic acid, probenecid, atazanavir, gemfibrozil, indinavir) of phase 2 drug metabolizing enzymes are prohibited within 14 days prior to first dose of NOX66 and the rest of the study.

- Based on *in vitro* data, idronoxil may inhibit the activity of cytochrome P450 (CYP) 2C8, CYP2C9, CYP2C19 and CYP3A4 enzymes in human microsomes in a range of 0.457 to 3000 µM and concomitant medication that is metabolized by these enzymes should be used with caution.
- The use of inhibitors of uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes should be avoided.
- Soya contains a high proportion of isoflavones which may interfere with the bioanalytical assay used for detection of idronoxil (active substance), itself an isoflavone derivative, in plasma and urine samples, thus within 2 days prior to NOX66 administration and for the entire duration of the first cycle of the study, patients must be on a soya free diet. The following types of foods are prohibited: edamame, meat alternatives, miso, soymilk, soy nuts, soy sauce (tamari, shoyu and teriyaki), tempeh, and textured soy protein. Trace or very small amounts of soy in foods are permitted.

#### 8.2.2.5 Calibration of Equipment

The Investigator (or qualified designee) is responsible for ensuring that any device or instrument used for a clinical evaluation/test during the study that provides information about eligibility criteria and/or safety or efficacy parameters is suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

### 8.2.3 Dose-limiting Toxicity

See Section 7.1.2.2 for details.

### 8.2.4 Physical Examinations

A complete physical examination will be performed at Screening. A symptom-directed physical examination will be performed prior to the first dose of study drug in Cycles 1 to 3, and every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.; or within 3 days before Day 1 of the cycle) and at the EOT/ED Visit. Physical examinations will include, at a minimum, assessments of the head, eyes, ears and throat and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, endocrine systems and perineal and anal region. Physical examinations need to include the assessment of the perineal and anal region. Height will be recorded at Screening only. Weight will be measured at Screening, Cycles 2 and 5 and every second cycle thereafter (i.e., Cycles 7, 9, 11 etc.).

Abbreviated physical examinations may be conducted as needed and will focus on new symptoms and will include examination of relevant systems as identified by the Investigator.

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

### 8.2.5 Vital Signs

Vital signs will be assessed as specified in the SoA (Table 1-1 [Parts 1 and 2]).

Oral or tympanic (both are acceptable) temperature, pulse, respiratory rate and blood pressure (BP) will be assessed at Screening and during Cycle 1 at the following timepoints: predose and at 1 and 4 hours postdose on Days 1, 6 and 14. Vital signs will be measured predose on Day 1 of Cycles 1 to 3, every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.) and at the EOT/ED Visit.

Blood pressure and pulse measurements will be assessed supine with a completely automated device. Manual techniques will be used only if an automated device is not available or to confirm automated readings, as needed.

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

Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse and one BP measurement (after the patient has been supine for 5 minutes).

### 8.2.6 Electrocardiograms

Triplicate 12-lead ECGs will be obtained in Parts 1 and 2 as outlined in the SoA (Table 1-1 [Parts 1 and 2]) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.

For all patients in Part 1 and the first 10 patients in each tumor type for Part 2 who will undergo PK sampling, a series of ECGs (in triplicate, within 1 to 2 minutes apart) will be collected at Screening, and at the following timepoints (Table 1-2):

- Cycle 1:
  - Days 1, 6 and 14: predose (within 30 minutes prior to dosing to allow for sitting BP if needed) and at 1, 2, 3, 4 and 6 hours postdose (+ 15 minutes). Additionally, for Part 1 only, ECGs will also be taken on Day 1 at 8 and 12 hours postdose (+ 15 minutes).
  - Day 2: predose.

- Cycle 2 Day 1: Predose (within 30 minutes prior to dosing to allow for sitting BP if needed) and at 1 hour postdose (+ 15 minutes).
- Cycle 3 Day 1: Predose (within 30 minutes prior to dosing to allow for sitting BP if needed) and at 1 hour postdose (+ 15 minutes).

For patients in Part 2 who will not undergo PK sampling, a series of ECGs (in triplicate, within 1 to 2 minutes apart) will be collected at Screening, and a single ECG predose (within 30 minutes prior to dosing to allow for sitting BP if needed) will be collected on Day 1 of Cycles 1 to 3.

Electrocardiograms will be taken predose (within 30 minutes prior to dosing to allow for sitting blood pressure if needed) for all patients in both study parts on Day 1 of every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.) and at the EOT/ED Visit. Electrocardiograms will be obtained after 5 minutes of rest in the supine position.

Twelve-lead ECGs will be obtained after the patient has been resting supine for at least 5 minutes prior to the times indicated in the SoA. All ECGs should be recorded with the patient in the same physical position.

At each time point at which triplicate ECG recordings are required, three individual ECG tracings should be obtained as closely as possible in succession, within 1 to 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

### 8.2.7 Clinical Safety Laboratory Assessments

Refer to Section 10.2 for the list of clinical safety laboratory tests to be performed and to the SoA (Table 1-1 [Parts 1 and 2]) for the timing and frequency. Clinical laboratory assessments will be done at Screening, Cycle 1 on Day 1 (or within 3 days before the first dose administration on Day 1), Days 6 and 14 (within 1 day before dose administration on each of Days 6 and 14), on Day 1 (or within 3 days of Day 1) of Cycles 2 and 3, every second cycle thereafter (i.e., Cycles 5, 7, 9, 11 etc.) and at the EOT/ED Visit.

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

All laboratory tests with values considered clinically abnormal during the study treatment period or within 30 days after the last dose of study drug should be repeated until the values return to

normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2 must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from laboratory assessments not specified in the protocol and performed at the institution's local laboratory result in the need for a change in patient management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification), then the results must be recorded in the eCRF.

### 8.2.8 Radiotherapy Treatment Interruptions

The frequency of radiotherapy treatment interruptions will be assessed by calculating the number of days of treatment interruptions over the study.

## 8.3 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

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

The Investigator and any qualified designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE and remain responsible for following up AE that are serious, considered related to the study drug or the study, or that caused the patient to discontinue the study drug or the study (see Section 7).

Adverse event questioning will include specific questions regarding symptoms of COVID-19: fever, cough, dry throat, difficulty breathing and potential exposure in the past 2 weeks.

Confirmed and suspected SARS-CoV-2 infection and COVID-19 will be recorded in the AE fields.

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

All AEs and SAEs will be collected from the signing of the ICF until 30 days after the last dose of study drug at the time points specified in the SoA (Table 1-1 [Parts 1 and 2]). Follow-up of AEs/SAEs after the last dose of study drug will be done by phone call.

Medical occurrences that begin before the first dose administration but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

### 8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

The severity of AEs will be classified into Grade 1 through 5 using the NCI-CTCAE v5.0. For details, refer to Section 10.3.3.

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

### 8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

### 8.3.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours, see Section 10.3) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.

The Sponsor and CRO have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.3.5 Pregnancy

If a female patient or a female partner of a male study patient who has been exposed to the study drug becomes pregnant, the pregnancy and outcome of pregnancy should be monitored. If a pregnancy in a female patient or a female partner of a male patient is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Pregnancy of the female patient or of the male patient's female partner alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Details of all pregnancies in female patients or female partners of male patients will be collected after the first dose administration and until 3 months after the last dose of NOX66. Information on the pregnancy of a female patient or of the male patient's female partner must be obtained directly from the female patient or the male patient's female partner. Therefore, prior to obtaining information on the pregnancy, the Investigator must obtain the consent of the female patient or the male patient's female partner.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

### 8.3.6 Cardiovascular and Death Events

Not applicable.

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

Not applicable.

### 8.3.8 Adverse Events of Special Interest

Not applicable.

## 8.4 Treatment of Overdose

For this study, any dose of NOX66 greater than 2400 mg within a 24-hour time period will be considered an overdose. If a patient takes more doses than the assigned doses within a 24-hour time period, this will also be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for AE/SAE and laboratory abnormalities until resolved or for up to 30 days (whichever occurs first).
3. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding whether the patient can continue the study will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

## 8.5 Pharmacokinetics

In Parts 1 and 2, blood samples of approximately 4 mL each will be collected for measurement of plasma concentrations of idronoxil and selected metabolites as specified in the SoA (Table 1-1 [Parts 1 and 2]). For Part 2, PK sampling will only occur for the first 10 patients enrolled in each tumor group (mCRPC, BC and NSCLC). A maximum of 31 samples will be collected at various time points during the study (see Table 1-3 for detailed sampling schedule) from each patient. Instructions for the collection and handling of PK samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF. If a bowel movement occurs during the collection period, the time of each bowel movement should be recorded, and the blood sample collections should continue as planned.

Plasma will be analyzed for the quantification of idronoxil and selected metabolites using a validated high-performance liquid chromatography and mass spectrometry methodology.

Each plasma sample will be divided into 3 aliquots (1 each for PK, other analyses, and a back-up) and stored according to the instructions in the Laboratory Manual. Samples collected for analyses of idronoxil plasma concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study. Pharmacokinetic parameters of idronoxil and selected metabolites will be determined by non-compartmental analysis. Pharmacokinetic sample analysis will be performed at a designated central laboratory.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files.

## 8.6 Pharmacodynamics

Please refer to Section 8.8 Biomarkers.

## 8.7 Genetics

The study will collect data from any available historical genetic assays conducted to identify genetic variations as part of the patients' medical history.

## 8.8 Biomarkers

Changes from baseline in the lipidomic profile, plasma levels of cytokines, chemokines (all sites) and circulatory tumor deoxyribonucleic acid (ctDNA; for all patients at pre-selected sites that have peripheral blood mononuclear cell isolation capabilities in Australia and the US only) will be assessed (Parts 1 and 2). These sample analyses will be performed at a designated central laboratory. In addition, lipidomic profiling, capturing over 300 lipid species, will be determined by liquid chromatography-tandem mass spectrometry on the plasma samples collected from the study patients. Samples for ctDNA analysis will not be collected from patients at sites in countries where this is not permitted by the regulatory authorities.

Blood samples of approximately 4 mL each will be collected for measurement of plasma cytokine, chemokine and lipid concentrations and approximately 10 mL each for ctDNA analysis as specified in Table 1-4.

Sampling for biomarker analysis will be performed at:

- Screening or Cycle 1 on Days 1 and 15

- Prior to Cycle 3 Day 1: This sample should be collected after the patient has completed 7 days of NOX66 treatment in Cycle 2, but before Day 1 of Cycle 3.
- EOT/ED Visit.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Each plasma sample will be divided into 3 aliquots (1 each for PD, other analyses, and a back-up) and stored according to the instructions in the Laboratory Manual.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to NOX66.

If there is any remaining plasma from these samples, the Sponsor may perform additional analyses for relevant biomarkers in the future. Taking part in this future research is optional. Patients will be asked to consent to their samples being used for this optional future research.

## 8.9 Archival and Fresh Tissue Biopsy

Patients will be asked whether they are willing to provide both archival and fresh tissue biopsy samples OR only fresh tissue biopsy if they do not have archival tissue samples. Available archival tissue samples will only be requested if a fresh tissue biopsy is collected after Cycle 3. Provision of a fresh biopsy sample and/or an archival tissue sample is optional. See Table 1-5.

## 8.10 Immunogenicity Assessments

Immunoassays will not be performed during this study.

## 8.11 Health Economics or Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 Statistical Considerations

## 9.1 Statistical Hypotheses

There will be no formal statistical hypotheses tested in this study. All analyses will be descriptive.

## 9.2 Sample Size Determination

The primary objective of this study is to characterize the safety and tolerability of NOX66 and thereby inform the RP2D of NOX66 for future clinical studies in patients with mCRPC and other solid tumors. Hence, for Part 1 and Part 2 the number of patients has been chosen with the aim to obtain adequate safety, tolerability, safety, PK, and PD profile data while exposing as few patients as possible to the study treatments and procedures.

The sample sizes selected for this study are as follows:

- Part 1 (Dose Escalation): Up to 30 patients will be enrolled in Part 1, in cohorts of 3 to 6 patients (Dose Cohort 1) or 3 to 8 patients (Dose Cohorts 2 to 4) at each specified dose.
- Part 2 (Dose Expansion): A total of 40 patients with mCRPC will be enrolled in Arm 1 and 24 to 30 patients (12 to 15 patients per tumor type [BC and NSCLC]) will be enrolled in Arm 2. The sample sizes for Part 2 were selected to provide sufficient observations for the estimation of endpoints and to assess any signal of efficacy following NOX66 and EBRT treatment.

## 9.3 Populations for Analyses

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

**Table 9-1 Populations for Analysis**

| Population (Analysis Set) | Description |
|---|---|
| Full Analysis Set (FAS) | The FAS comprises all patients who received at least one dose of study drug. |
| Safety Analysis Set | The Safety Analysis Set consists of all patients who received at least one dose of study drug. In this study, the Safety Analysis Set will be the same as the FAS.<br>This analysis set will be the primary analysis set for all safety endpoints. |
| Per Protocol Set (PPS) | The PPS consists of all patients in the FAS with ≥ 80% treatment compliance and without major protocol deviations. |
| PK Analysis Set | The PK analysis set consists of all patients in the Safety Analysis Set and who have at least one idronoxil or metabolite plasma concentration value. |
| Biomarker Analysis Set | The Biomarker Analysis Set consists of all patients in the Safety Analysis Set and who have at least one plasma biomarker concentration value. |

Separate summaries may be provided for patients participating in Parts 1 and 2.

## 9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized prior to database lock. Below is a description of planned statistical analyses. Further details are presented in the SAP.

### 9.4.1 General Considerations

The main aims of the study are to assess the safety, tolerability, efficacy, PK and PD profiles of idronoxil (and selected metabolites) and EBRT in combination with NOX66 in patients with prostate cancer and other solid tumors.

Concomitant medications, treatment exposure and study drug compliance will be summarized by dose cohort for Part 1 and by treatment arm for Part 2. All summaries will be based on the Safety Analysis Set.

Continuous data will be summarized using the number of patients (n), mean, standard deviation, median, 25$^{th}$ and 75$^{th}$ percentiles, minimum and maximum. Categorical data will be summarized using frequency tabulations (number and percentage of patients).

Unless specified, no formal statistical hypothesis testing will be conducted and all analyses will be descriptive. Two-sided 95% confidence intervals (CIs) will be presented alongside all point estimates to access precision.

Baseline will be defined as the last measurement obtained prior to the first administration of NOX66.

All statistical analysis will be performed using Statistical Analysis Software (SAS®) Version 9.3 or higher.

### 9.4.2 Participant Disposition

The disposition of all patients who sign an ICF will be provided. The number of patients screened, enrolled, who received study drug, completed and discontinued will be summarized as well as the reason(s) for screening failure and all post-enrollment study or study drug discontinuations.

### 9.4.3 Participant Demographics and Baseline Characteristics

Participant demographics and baseline characteristics will be summarized separately for each study part using appropriate descriptive statistics. Demographics and baseline characteristics

will be summarized for Part 1 by dose cohort and will be based on the Full Analysis Set (FAS). For Part 2, demographics and baseline characteristics will be summarized by treatment arm and will be based on the FAS.

Relevant medical history will be summarized in the same manner as described above.

### 9.4.4 Concomitant Medications

Concomitant medications will be summarized separately for each study part. All concomitant medications will be recorded in the eCRF and will be coded based on World Health Organization drug dictionary latest version. Descriptive summaries will be provided by coded term.

### 9.4.5 Treatment Exposure and Study Drug Compliance

Extent of exposure to NOX66 will include the following variables:

- Total treatment duration (in weeks) = (date of last treatment – date of first treatment + 1)/7.
- Relative Dose Intensity = 100 * (number of suppositories received/planned number of suppositories for duration of treatment).

A record of the number of NOX66 suppositories dispensed to and taken by each patient will be documented. The proportion of suppositories taken will be calculated and patients will be deemed compliant if this proportion is ≥ 80%.

For EBRT, the date and time of each dose administered will be listed. The site coordinator will confirm this information with the radiologist administering the EBRT and the date of administration will be added to the electronic data capture (EDC) system.

### 9.4.6 Primary Endpoint(s)

#### 9.4.6.1 Part 1 (Dose Escalation): Recommended Phase 2 Dose

The primary endpoint for Part 1 (dose escalation) is the number of DLTs, which will be used to estimate the MTD and select the RP2D. This will be determined by the dose level at which no more than 1 patient out of 6 patients experiences a DLT during Cycle 1.

For assessment of DLTs, toxicities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v22.0 or higher and graded according to NCI-CTCAE v5.0. See Section 7.1.2.2 for details on DLT criteria.

The number of DLTs experienced by a patient will be summarized by DLT type for each dose cohort and DLT events will be listed by patient. The listing will include the description, severity and relationship of the events to study drug.

#### 9.4.6.2 Part 2 (Dose Expansion)

The primary endpoints for Part 2 (dose expansion) are:

- Arm 1 (mCRPC): The proportion of patients who achieve ≥ 30% reduction in PSA from baseline at the end of Cycles 3 and 6.
- Arm 2 (BC and NSCLC): Disease control rate assessed by determining the percentage of patients with CR, PR, plus SD.

For patients with mCRPC, plasma levels of PSA will be collected on Day 1 of Cycles 1 to 5, every second cycle thereafter (i.e., Cycles 7, 9, 11 etc.), at the EOT/ED Visit and at the 6-, 9- and 12 month Follow-up Visits for all patients including those that discontinued for any reason other than disease progression. The number and proportions of patients with a ≥ 30% reduction in PSA levels from baseline to the end of Cycles 3 and 6 (primary endpoint) and change from baseline at any time point (secondary endpoint) will be presented for Treatment Arm 1 along with the corresponding exact 95% CI (Clopper-Pearson).

The effect of NOX66 on DCR will be assessed based on the percentage of patients with the best overall response of CR or PR at any time plus SD from first dose administration until disease progression, death due to any cause or the start of new anticancer therapy, respectively. RECIST v1.1 criteria will be applied to assess CR, PR and SD. Disease control rate will be presented for Treatment Arm 2 along with the corresponding exact 95% CI (Clopper-Pearson). Tumor imaging and disease response assessments will be performed for up to 12 months after the last dose of study drug until disease progression, withdrawal of consent, initiation of new anticancer therapy, the patient is lost to follow-up or death, whichever comes first.

### 9.4.7 Secondary Endpoint(s)

#### 9.4.7.1 Safety of NOX66 and Both Doses of EBRT

Safety profiles will be summarized by NOX66 dose cohort and separately by EBRT dose cohort (Part 1) or treatment arm and separately by EBRT dose cohort (Part 2) and will be based on the Safety Analysis Set.

Adverse events will be coded using the MedDRA v22.0 or higher and will be graded according to the NCI-CTCAE v5.0. Treatment-emergent AEs are defined as those AEs that either start or

worsen in severity on or after the date of first administration of study drug and on or before 30 days after the last dose of study drug.

Treatment-emergent AEs will be summarized by severity grade and relationship to study drug. Serious AEs, serious TEAEs and TEAEs leading to discontinuation of study drug or to death will be presented.

Changes in clinical laboratory values, vital signs, ECGs and physical examinations will be summarized over time.

### 9.4.7.2 Efficacy of NOX66

The following efficacy analysis will be conducted for the patients enrolled to Part 1 and Part 2 of the study. All analyses are based on the FAS. Results will be summarized by dose cohort (Part 1) or treatment arm (Part 2).

For patients with mCRPC, the change in PSA from baseline will be summarized by dose cohort (Part 1) or treatment arm (Part 2, Arm 1) assessed using samples collected on Day 1 of Cycles 1 to 5, every second cycle thereafter (i.e., Cycles 7, 9, 11 etc.), at the EOT/ED Visit and at the 6-, 9- and 12-month Follow-up visits for all patients including those that discontinued for any reason other than disease progression. A PSA response will be considered as a PSA value reduction ≥ 30% from baseline at the end of Cycles 3 and 6. A PSA reduction from baseline at any time point will also be assessed as a secondary objective.

Overall response rate, defined as the percentage of patients with CR and PR, will be assessed based on change from baseline imaging (RECIST v1.1 and PCWG-3 criteria for measurable or evaluable lesions). The number and proportion of responders (CR and PR) will be presented along with the exact 95% CI (Clopper-Pearson) for the time points after Day 1. Patients are allowed to continue study treatment until disease progression, unacceptable toxicity, withdrawal of consent, start of a new anticancer therapy, withdrawal of the patient by the Investigator or termination of the study by Sponsor. Tumor imaging assessment will be continued as scheduled for the patients who are discontinued from the study for reasons other than disease progression (see Section 8.1.3). The best overall response (CR, PR, SD or progression) will be summarized.

The change in ECOG from baseline will be summarized by dose cohort (Part 1) or treatment arm (Part 2) over time. The change in pain severity and pain interference with daily activities from baseline will be summarized by dose cohort (Part 1) or treatment arm (Part 2) over time. The number and proportion of patients with a pain response (≥ 2-point reduction in pain severity and no additional opioid use) will be summarized over time along with the exact 95% CIs

(Clopper-Pearson). The time to morphine administration and/or use of analgesics together with change from baseline assessment will be calculated and summarized by dose cohort (Part 1) and treatment arm (Part 2). The number and proportion of patients with SREs and/or SSEs will be summarized at each time point and presented along with the exact 95% CI (Clopper-Pearson).

Quality of Life analyses will be performed for the Safety Analysis Set. Scale measures from the EORTC-QLQ-C30, BPI-SF, PEQ, and FACT-P (mCRPC patients only) will be summarized for all patients by dose at each on-site visit as well as the change from baseline to each on-site visit.

Survival functions will be computed for OS, PFS and PSA reduction/progression (for Part 2, Arm 1 only) using the Kaplan-Meier method. Estimates of median survival times will be presented by dose cohort (Part 1) or treatment arm (Part 2) along with 2-sided 95% CIs. The $25^{th}$ and $75^{th}$ percentiles and the range (minimum, maximum) will be presented as well.

Duration of response is defined as the time from the first documented overall response of CR, PR or SD to the first documented overall response of progressive disease. This will be estimated using the Kaplan-Meier method. Estimates of median survival times will be presented along with the two-sided 95% CI. The $25^{th}$ and $75^{th}$ percentiles and range (minimum, maximum) will also be presented.

### 9.4.7.3 Pharmacokinetic Evaluation

Plasma samples will be assayed for idronoxil and up to 7 selected metabolites by validated LC-MS/MS. Individual plasma concentration-time data and plasma PK parameters will be summarized using descriptive statistics by treatment day and sampling time for idronoxil and the 7 detectable metabolites (GIS/SIG, IG, GI, IS, SI, SIS, and GIG). Plasma PK parameters will be determined by noncompartmental analysis for idronoxil and selected metabolites (SI, IS, GI, IG, SIG/GIS, GIG, SIS) and will be summarized by dose and treatment day.

The following PK parameters will be estimated for idronoxil and the selected metabolites following the morning dose on Days 1, 6 and 14 of Cycle 1, as data permit: $C_{max}$, $C_{min}$ (predose), $T_{max}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}6)}$, $AUC_{(0\text{-}12)}$, $AUC_{(0\text{-}inf)}$ and $t_{½}$. Details of the analyses will be included in the SAP.

Dose proportionality will be assessed using the power model for $C_{max}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}6)}$, and $AUC_{(0\text{-}12)}$ on Days 1, 6 and 14 of Cycle 1 for the parent compound.

If data permits, accumulation ratios will be calculated for parent compound and selected metabolites for $C_{max}$, $C_{min}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}6)}$, and $AUC_{(0\text{-}12)}$ for Days 6 and 14 of Cycle 1 (e.g., Day 14/Day 1 and Day 6/Day 1) and Day 8 of Cycles 2 and 3.

The metabolite to parent ratios will be calculated (as data permit) for Days 1, 6 and 14 of Cycle 1, for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-6)}$, and $AUC_{(0-12)}$ and for single time points on Day 1 of Cycles 2 and 3.

Concentration and PK parameter data will be listed, summarized and plotted. Details of these analyses will be included in the SAP.

There are no formal PK parameters for concentration data from Cycles 2 and 3 because these are single time points. However, metabolite to parent ratios will be explored.

Exploratory analyses of the relationship between plasma concentrations of parent drug and selected metabolites and/or PK parameters and AEs or PD biomarkers may be assessed by graphical methods and special summary tables. Exposure-response relationship may also be explored.

#### 9.4.7.4 Pharmacodynamic Biomarker Analysis

Plasma levels of cytokines and chemokines will be evaluated as part of the PD analysis. Using the plasma samples, analysis will be performed for ctDNA and lipidomic profiling.

Absolute and change from baseline results of biomarker analysis will be summarized descriptively and also presented on a plot.

### 9.5 Interim Analyses

No formal interim analyses are planned.

### 9.6 Data Monitoring Committee (DMC)

A DMC will not be appointed. Patient safety and scientific integrity of the study will be monitored by the SSC.

## 10 Supporting Documentation and Operational Considerations

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

#### 10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.

- Applicable International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
  - Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

### 10.1.2 Financial Disclosure

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

### 10.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

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

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

Patients who are rescreened are required to sign a new ICF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

### 10.1.4 Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

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

### 10.1.5 Committees Structure

An SSC will be responsible for reviewing all safety data (see Section 7.1.2.1).

### 10.1.6 Dissemination of Clinical Study Data

All clinical study findings and documents will be regarded as confidential. Study documents (protocol[s], IBs and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent

necessary to obtain informed consent from patients who wish to participate in the clinical study or to comply with regulatory requirements.

The anonymity of participating patients must be maintained. Patients will be specified on study documents (except patient identification Code List Log) by their patient number and year of birth, not by name. The year of birth data will also be available to external study team members (e.g., collected on eCRF, central laboratory sample tubes and laboratory documents). Documents that identify the patient (e.g., the signed ICF) must be maintained in confidence by the Investigator.

The clinical study may be considered for publication in the scientific literature irrespective of whether the results of the clinical study are positive or negative (Section 10.1.10). In addition, the results of clinical studies will be provided on the publicly funded website www.ClinicalTrials.gov in line with the applicable regulations.

### 10.1.7 Data Quality Assurance

- All patient data relating to the study will be recorded on the eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategies (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., CRO).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator after study completion following local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.
- If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.
- The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

#### 10.1.7.1 Quality Assurance and Control

The Sponsor is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted, and data are generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

The Sponsor or Sponsor's designee may arrange to audit the study at any or all study sites and facilities. The audit may include on-site review of regulatory documents, eCRFs and source documents. Direct access to these documents will be required by the auditors.

### 10.1.8 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

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

### 10.1.9 Study and Site Start and Closure

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

The first act of recruitment is the first site open and will be the study start date.

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

The Sponsor may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study drug development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

### 10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor at least 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

### 10.1.11 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In addition, for the US, following above mentioned approval, the protocol amendment(s) will be submitted to the investigational new drug (IND) under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

### 10.1.12 Liability and Insurance

The Sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The insurance will cover any injury related to the study drug and clinical study experienced by the patient (if the patient followed all protocol procedures and restrictions). The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

Details are provided in the ICF.

#### 10.1.12.1 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC/eCRF entries and individual patient's medical records, assess study drug accountability and ensure that the study is being conducted according to pertinent regulatory requirements. EDC/eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the EDC/eCRF entries for completeness and clarity and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures Parexel and the Sponsor of the necessary support at all times.

## 10.2 Appendix 2: Clinical Safety Laboratory Tests

The tests detailed in Table 10-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in Sections 5.1 and 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

**Table 10-1 Protocol-Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet Count<br>RBC Count<br>Hemoglobin<br>Hematocrit | RBC Indices:<br>MCV<br>MCH<br>%Reticulocytes | WBC count with Differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Clinical Chemistry[1] | BUN/Urea<br>Creatinine<br>Glucose (fasting or non-fasting)<br>$CO_2$/Bicarbonate<br>Uric acid | Potassium<br>Sodium<br>Calcium<br>Chloride<br>Magnesium<br>Phosphate/ Phosphorus | AST<br>ALT<br>ALP<br>LDH<br>GGT | Total and direct bilirubin<br>Albumin<br>Total cholesterol<br>Triglycerides |
| Coagulation | Prothrombin time, INR, aPTT | | | |
| Routine Urinalysis | Specific gravity, pH, glucose, protein, blood, ketones, urobilinogen, bilirubin, nitrite, WBCs, blood, creatinine (by dipstick)<br>Microscopic examination (if blood or protein is abnormal) | | | |
| Serology | HIV, HBsAg, anti-HBc and HCV antibody | | | |
| Baseline/Ongoing medical castration (mCRPC patients only) | Testosterone levels | | | |
| COVID-19 Testing (optional) | SARS-CoV-2 RT-PCR[2] | | | |

| Laboratory Assessments | Parameters |
|---|---|
| Pregnancy Testing | Highly sensitive serum (Screening) and urine (other time points) human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)[3] |

NOTES:

1 All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2 To be assessed at Screening, each admission and may optionally be done at additional time points at the discretion of the Investigator.
3 Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; anti-HBc = hepatitis B core antibody; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; $CO_2$ = carbon dioxide; GGT = gamma glutamyl transferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IEC = Independent Ethics Committee; INR = international normalized ratio; IRB = Institutional Review Board; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory coronavirus 2; ULN = upper limit of normal; WBC = white blood cell

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

## 10.3.1 Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of a study drug, whether or not considered related to the study drug.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug. |
| **Events Meeting the AE Definition** |
| • Any abnormal laboratory test results (hematology, clinical chemistry or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (e.g., not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.<br>• Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.<br>• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. |

| Events NOT Meeting the AE Definition |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.<br>• The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

### 10.3.2 Definition of SAE

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

| An SAE is defined as any untoward medical occurrence that, at any dose: |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Other situations**

- Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive intervention 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.

### 10.3.3 Recording and Follow-up of AE and SAE

**AE and SAE Recording**

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

**Assessment of Intensity**

The Investigator will make an assessment of severity for each AE and SAE reported during the study and classify it into one of Grade 1 through 5 using the NCI-CTCAE v5.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as Grade 3 or higher.

**Assessment of Causality**

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AE and SAE**

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.

- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

### 10.3.4 Reporting of SAE

For studies in the US:
The Investigator must report any SAEs in the eCRF/EDC system within 24 hours of becoming aware of the event. In the event the EDC system is down, the Investigator must complete the SAE form and provide the completed form to the Parexel Clinical Studies Safety Center using the email address provided to the sites on the eCRF/SAE form.

When sending the completed SAE form via email, state that you are reporting an SAE and give the Investigator's name, your name, the telephone number where you can be reached and the protocol number and title. The event must be documented in the eCRF/EDC system when it is back online.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/Parexel will evaluate the seriousness and the causal relationship of the event to study drug. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference document (IB or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be recorded from signing of informed consent until 30 days after the last dose of study drug. Serious adverse events occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally-related to study drug.

***SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS***

Parexel International Corporation
Clinical Studies Safety Center
Medical Monitor
Drug Safety Specialist
(See SAE Reporting Instructions)

1. Telephone the Medical Monitor using the number provided to sites to inform him/her that you have completed the SAE eCRF page/SAE form. If the Medical Monitor is not available or you are calling after business hours (8:30 am to 5:30 pm Eastern time, Monday to Friday), leave a message in his/her voice mailbox.
2. Provide the Medical Monitor with the Principal Investigator's name, your name, the telephone number where you can be reached and the protocol number and title.
3. Inform the Medical Monitor within 24 hours of becoming aware of the event and provide any supporting documentation to him/her within this time frame.
4. After business hours, the Medical Monitor may be reached through Parexel's 24-hour answering service on the number provided to the sites. Give the answering service the protocol number, the study drug name and the Sponsoring pharmaceutical company.

For Studies in the EU:

All SAEs that occur during the study and all SAEs occurring up to 30 days after receiving the last dose of study drug, whether considered to be associated with the study drug or not, must be reported within 24 hours in the eCRF/EDC system. If the EDC system is offline for any reason, the Investigator should complete the SAE form and provide the completed form to the Parexel Safety Contact using the email address provided to the sites.

SAEs occurring after the end of the study should be reported to the Sponsor/Parexel by the Investigator if the Investigator considers there is a causal relationship with the study drug.

The minimum information required for an initial report is (in situations where the EDC system is offline at time of reporting):

- Name of person sending the report (e.g., name, address of Investigator).
- Patient identification (Screening/participant number, initials, NOT patient name).
- Protocol number.

- Description of SAE.
- Causality assessment, if possible.

However, as far as possible all points on the SAE form should be covered in the initial report or the completed SAE form itself must be emailed to the Parexel Safety Contact using the information provided to study sites. The original SAE form must then be sent by mail to the Parexel Safety Contact. In addition, the event must be documented in the eCRF/EDC system when it is back online.

In case the Parexel Safety Contact cannot be contacted (e.g., out of normal working hours or at weekends), an automated reporting service is available. The required information should be emailed, and a message should be left on the voicemail service (the relevant phone number/email address will be provided to all sites).

After receipt of the initial report, the safety center will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. Parexel will be responsible for all information processing and reporting according to local legal requirements. Where necessary, Investigators will inform regulatory authorities in their own countries.

For Studies in Australia:

The Investigator must report any SAEs in the eCRF/EDC system within 24 hours of becoming aware of the event. In the event the EDC system is down, the Investigator must complete the SAE form and provide the completed form to the Parexel Clinical Studies Safety Center using the email address provided to the sites on the eCRF/SAE form. The original SAE form must be sent by mail to the Parexel Safety Contact and the event must be documented in the eCRF/EDC system when it is back online.

All SAEs will be recorded from signing of informed consent until 30 days after the last dose of study drug. Serious adverse events occurring after the end of the study should be reported to the Sponsor/Parexel by the Investigator if the Investigator considers there is a causal relationship with the study drug.

The minimum information required for reporting of an SAE is (in situations where the EDC system is offline at the time of reporting):

- Contact details of the person sending the report (e.g., name, address, phone number).
- Patient identifier (e.g., Screening/participant number, initials, date of birth, but not their full name).

- Details of the product involved.
- Protocol number.
- Details of the suspected SAE (including causality and severity assessment).

In case the Parexel Safety Contact cannot be contacted (e.g., out of normal working hours or at weekends), an automated reporting service is available. The required information should be emailed, and a message should be left on the voicemail service (the relevant phone number/email address will be provided to all sites).

After receipt of the initial report, the safety center/Sponsor will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action. Parexel will be responsible for all information processing and reporting according to local legal requirements. Where necessary, Investigators will inform regulatory authorities in their own countries.

## 10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

### Definitions

### Woman of Childbearing Potential

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose administration, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

      NOTE: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement (> 40 IU/L) is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

**Contraception Guidance**

**Male Patients:**

Male patients who have had a vasectomy may participate in this study provided that the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Male patients with female partners of childbearing potential are eligible to participate if the agree to ONE of the following during the protocol-defined time frame in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male patients must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study drug.

Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

**Female Patients**

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below, and to not donate ova, for 3 months after the last dose of study drug.

| **Highly Effective Contraceptive Methods That Are User Dependent**[1]<br>*Failure rate of < 1% per year when used consistently and correctly.* |
|---|
| Combined (estrogen- and progestin-containing) hormonal contraception associated with inhibition of ovulation[2]<br>• Oral<br>• Intravaginal<br>• Transdermal |

| **Highly Effective Contraceptive Methods That Are User Dependent[1]**<br>*Failure rate of < 1% per year when used consistently and correctly.* |
|---|
| Progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Injectable |
| Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[2]<br>• Intrauterine device<br>• Intrauterine hormone-releasing system |
| **Vasectomized Partner**<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. |
| **Sexual Abstinence**<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient. |

NOTES:

1 Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

2 Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 6 months after the last dose of study drug.

## Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Pregnancy testing will be performed according to the standard procedures of the study site.
- Additional pregnancy testing should be performed during the treatment period (at the discretion of the Investigator). During the Follow-up Visit period (up to 3 months after last dose of study drug), patients will be questioned about their pregnancy status and use of contraception.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

**Collection of Pregnancy Information:**

**Male Patients with Partners Who Become Pregnant**

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive NOX66.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 3 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

**Female Patients Who Become Pregnant**

- The Investigator will collect pregnancy information on any female patients who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect any follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of the pregnancy will be reported, regardless of fetal state (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to study drug by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study drug or will be withdrawn from the study.

## 10.5 Appendix 5: Tumor Imaging

The revised RECIST guideline (version 1.1) will be used for assessment of tumor response in soft tissue lesions. While either CT or MRI may be utilized, as per RECIST v1.1, CT is the preferred imaging technique in this study.[6]

Bone lesions (mCRPC patients only) will be assessed using PCWG-3[7] criteria.

# 10.6 Appendix 6: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients (EORTC-QLQ-C30)

ENGLISH

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

ENGLISH

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

## 10.7 Appendix 7: Brief Pain Inventory – Short Form

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

**Brief Pain Inventory (Short Form)**

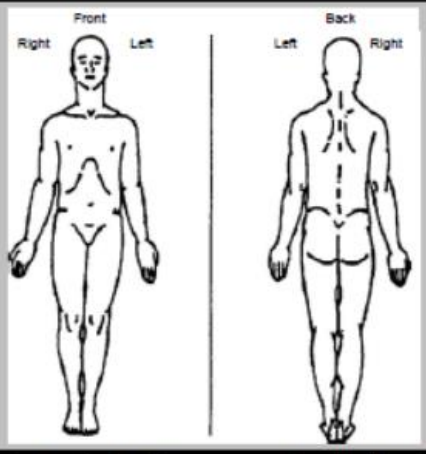
Date:____/____/____ Time:_____

Name:_____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.




3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ___/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

**7. What treatments or medications are you receiving for your pain?**

**8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.**

| 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
|---|---|---|---|---|---|---|---|---|---|---|
| No Relief | | | | | | | | | | Complete Relief |

**9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:**

**A. General Activity**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does not Interfere | | | | | | | | | | Completely Interferes |

**B. Mood**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does not Interfere | | | | | | | | | | Completely Interferes |

**C. Walking Ability**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does not Interfere | | | | | | | | | | Completely Interferes |

**D. Normal Work (includes both work outside the home and housework)**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does not Interfere | | | | | | | | | | Completely Interferes |

**E. Relations with other people**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does not Interfere | | | | | | | | | | Completely Interferes |

**F. Sleep**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does not Interfere | | | | | | | | | | Completely Interferes |

**G. Enjoyment of life**

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does not Interfere | | | | | | | | | | Completely Interferes |



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# 10.8 Appendix 8: Patient Experience Questionnaire (PEQ)

Protocol Number: NOX66-005 Page 1 of 4

**PEQ - Patient Experience Questionnaire**

| | | | |
|---|---|---|---|
| **Date of completion:** | __ __/__ __/20__ __<br>D D / M M / Y Y Y Y | **Subject ID:** | __ __ __ __ /__ __ __ |
| **Cycle number or visit name:** | | **Day number (if applicable):** | |

**Instructions:**

The questions below are to be answered based on your experience of administering NOX66 (the study drug) to date. You will be requested to complete this questionnaire **in full** the day after you start your first dose of the study drug, on the first day of your third treatment cycle, and at your End of Treatment or Early Discontinuation visit. The information you provide in this questionnaire will be kept strictly confidential.

Some questions require simple YES or NO answers, other questions are to be rated along a range from best on the left to worst on the right. Please **circle the number** that best corresponds with how you have felt, regarding the questions asked.

There are 10 questions and it should take you no more than 5 minutes to complete your answers.

Your effort is very much appreciated.

---

**Questions:**

1) **Have you inserted your last NOX66 suppository by yourself or was it inserted by someone else (e.g., your care giver, nurse)?**

Myself / Someone else

If you answered 'Myself', please go to **question 2**.

If you answered 'Someone else', please go to **question 3**.

2) **Ease of use: I found the process of inserting the suppository to be**

 

Very easy-------1------2------3------4------5------6------7------8------9------10------ Very difficult

3) **Comfort: I found the process of insertion of the suppository to be**

 

Very comfortable -------1------2------3------4------5------6------7------8------9------10------ Very uncomfortable

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**PEQ - Patient Experience Questionnaire**

| | | | |
|---|---|---|---|
| **Date of completion:** | __ __/__ __/20__ __<br>D D / M M / Y Y Y Y | **Subject ID:** | __ __ __ __ /__ __ __ |
| **Cycle number or visit name:** | | **Day number (if applicable):** | |

**4) Was there any pain associated with the insertion?**

No / Yes

**If 'Yes', I found the insertion of the suppository**


Minimally painful -------1------2------3------4------5------6------7------8------9------10------ Maximally painful

**5) Did you notice or feel the suppository after it has been in your body for more than 1 hour (e.g., the sensation of a foreign body)?**

No / Yes

**If 'Yes', I felt the suppository in my body**

None of the time *(after 1 hour)* -------1------2------3------4------5------6------7------8------9------10------ All the time

**If 'Yes', I found feeling the suppository in my body**


Not bothersome at all -------1------2------3------4------5------6------7------8------9------10------ Maximally bothersome

**6) Were your day-to-day activities (such as washing yourself, brushing your teeth, cooking, cleaning, working or leaving the home) impacted by the suppository?**

No / Yes

**If 'Yes', I found the suppository impacted my day-to-day activities**


Not at all -------1------2------3------4------5------6------7------8------9------10------ Very much

**PEQ - Patient Experience Questionnaire**

| | | | |
|---|---|---|---|
| **Date of completion:** | __ __/__ __/20__ __<br>D D / M M / Y Y Y Y | **Subject ID:** | __ __ __ __ / __ __ __ |
| **Cycle number or visit name:** | | **Day number (if applicable):** | |

**7) Did the suppository leak (e.g., staining of your underpants)?**

No / Yes

**If 'Yes', I found the leakage of the suppository**


Not bothersome at all-------1------2------3------4------5------6------7------8------9------10------ Very bothersome

**8) Were you worried about using a suppository before you entered the study?**

No / Yes

**If 'Yes', I found the idea of using a suppository**


Not worrisome at all-------1------2------3------4------5------6------7------8------9------10------ Very worrisome

**9) Are you concerned about continuing to use a suppository for the rest of the study?**

No / Yes

**If 'Yes', I find the idea of having to continue using a suppository**


Not worrisome at all-------1------2------3------4------5------6------7------8------9------10------ Very worrisome

**10) My overall experience using the suppositories has been**


Very good -------1------2------3------4------5------6------7------8------9------10------ Very bad

**PEQ - Patient Experience Questionnaire**

| | | | |
|---|---|---|---|
| **Date of completion:** | __ __/__ __/20__ __<br>D D / M M / Y Y Y Y | **Subject ID:** | __ __ __ __ / __ __ __ |
| **Cycle number or visit name:** | | **Day number (if applicable):** | |

**Please do NOT use the space below to record any side effect you experience during this study, please inform your study doctor or the study staff at the earliest time.**

**If you would like to add any additional feedback on your experience with NOX66, please add below:**

_____

_____

_____

_____

**Thank you very much!**

## 10.9 Appendix 9: Functional Assessment of Cancer Therapy – Prostate (FACT-P) Version 4

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | PHYSICAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | EMOTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| P1 | I have aches and pains that bother me | 0 | 1 | 2 | 3 | 4 |
| P2 | I have certain parts of my body where I experience pain | 0 | 1 | 2 | 3 | 4 |
| P3 | My pain keeps me from doing things I want to do | 0 | 1 | 2 | 3 | 4 |
| P4 | I am satisfied with my present comfort level | 0 | 1 | 2 | 3 | 4 |
| P5 | I am able to feel like a man | 0 | 1 | 2 | 3 | 4 |
| P6 | I have trouble moving my bowels | 0 | 1 | 2 | 3 | 4 |
| P7 | I have difficulty urinating | 0 | 1 | 2 | 3 | 4 |
| BL2 | I urinate more frequently than usual | 0 | 1 | 2 | 3 | 4 |
| P8 | My problems with urinating limit my activities | 0 | 1 | 2 | 3 | 4 |
| BL5 | I am able to have and maintain an erection | 0 | 1 | 2 | 3 | 4 |

## 10.10 Appendix 10: Guidance for Low-Dose EBRT

**Simulation and Motion Management**

Simulation study using either CT or MRI +/- PET scans should be carried out as part of treatment planning. The imaging will be performed to acquire the anatomy involved in the treatment with at least 5 cm of additional margin outside the planned radiation field to allow for adequate dose calculations. The simulation scan will be used to identify the lesion(s) and surrounding normal critical organs to develop a treatment plan to deliver radiation in a manner that targets the lesion(s) accurately and spares critical organs as much as possible. The simulation needs to account for tumor mobility and the scan techniques, where applicable, need to account for respiration, cardiac function, peristaltic activity, and organ filling and emptying.

The utilization of 4D simulation technique will be at the treating physician discretion when treating 8 Gy in 1 fraction or 20 Gy in 4 fractions. When treating with 25 Gy in 5 fractions, 4D simulation technique will be required in non-spinous lesions within 10 cm (either inferior or superior) of the diaphragm. When 4D simulation technique is utilized multiple images will be acquired and regular points along the patients breathing cycle utilizing equipment and practices detailed by treatment site SOPs. An internal gross tumor volume (iGTV) will be contoured to encompass the full range of tumor motion to be utilized for treatment planning purposes. It will be up to the treating physician's discretion to use techniques to reduce tumor motion and facilitate tumor tracking. These techniques include breath-hold, abdominal compression, and fiducial marker placement.

Guidelines described here will be superseded by any site-specific SOPs that require a higher degree of stringency.

**Immobilization**

Any immobilization equipment used must be fit for purpose. When immobilizing the patient in preparation for treatment, it is necessary to ensure the patient is as comfortable as possible and is in a stable position. This position needs to be reproducible at the time of treatment.

Immobilization techniques must take into account the individual patient needs, organ motion and the complexity of the proposed radiation therapy technique. Given treatment center variations in immobilization techniques, treatment-site SOPs will be followed regarding specific device utilization. These devices include customized devices such as thermoplastic masks and vacuum-assisted immobilization devices (e.g., Vac-Lok), placement of radiopaque markers and marking tattoos, and non-custom devices such as wing board and MedTec devices.

Comprehensive documentation that itemizes patient immobilization methods and set-up details is required to ensure that the optimal treatment position is achieved and reproducibility errors are minimized.

**Treatment Planning and Verification**

- Dose prescribed will be 8 Gy in 1 fraction or 20/25 Gy in 5 fractions, aiming to cover at least 99% of the PTV by 95% of the prescribed dose
- No 'hotspots' within or outside of the PTV to exceed 110% of prescribed dose

Treatment planning will include imaging procedures that will localize, delineate, and define target volumes and organs at risk, as well as enabling treatment verification. This should be done according to the institutional SOP and allow both forward and inverse planning techniques where appropriate.

Treatment planning needs to include:

- Positioning and immobilization
- Use of optimal imaging modalities
- Delineation of treatment fields and isocenters
- Measurements and patient contouring
- Documentation
- Patient consent to perform permanent skin marking procedures

Treatment verification needs to match the simulated/planned treatment parameter with that set on the treatment unit. The position of the treatment isocenters, radiation treatment field and/or its shape or anatomical volume must be evaluated against that determined in the treatment planning process.

The EBRT to be administered in the context of this study is for symptomatic relief and pain management, and not for the purpose of ablative therapy. As such, the prescribed EBRT should only be given to target lesions and normal tissues should be spared. If 25 Gy in 5 fractions is prescribed, it will be encouraged but not required that daily kV or MV imaging is obtained with every fraction and that on-board axial imaging is obtained on the first day of treatment.

For 25 Gy in 5 fractions, images must be obtained for image guidance prior to each fraction to verify proper beam alignment.

**Normal Tissue Constraints**

In the context of this study, it is a requirement that the radiation oncologist will follow the QUANTEC Guidelines for normal tissue constraints when administering low-dose EBRT (20 Gy in 5 fractions or 8 Gy in 1 fraction) to metastatic lesions[7]. For 25 Gy in 5 fractions, the dosing guidance from the AAPM Task Force Group 101 has to be followed[2]. This study will be excluding all patients who have central nervous system involvement; therefore, the CNS tissue tolerances, with the exception of spinal cord exposure, will not be included in the guidance on normal tissue dose constraints as set out below. These constraints are for EBRT at low dose and for standard fractionation.

| Tissue / Organ | Tissue radiation dose constraints (maximum radiation dose) |
|---|---|
| Spinal cord | 23 Gy |
| Retina | < 50 Gy |
| Cochlea | ≤ 45 Gy |
| Single parotid gland sparing | < 20 Gy |
| Irradiation to 2 parotid glands | < 25 Gy (spread across 2 glands) |
| Mandible | ≤ 70 Gy |
| Pharyngeal constrictors | < 50 Gy |
| Larynx | < 44 Gy |
| Brachial plexus | < 60 Gy |
| Lung | 20 Gy |
| Oesophagus | < 34 Gy |
| Heart | < 26 Gy |
| Liver | ≤ 28 Gy |
| Kidney | < 18 Gy per kidney |
| Stomach | < 50Gy |
| Small bowel (irradiation to less than one-third) | 50 Gy |
| Rectum | < 27 Gy |
| Skin | 40 Gy |
| Bladder | < 65 Gy |
| Femoral head | < 52 Gy |

**Equipment**

Radiation delivery equipment needs to have undergone appropriate dosimetry calibration using an acceptable phantom to ensure that the correct treatment beam energies are being generated, correct alignment between on-board imaging and treatment isocenter, and accurate motion of the treatment couch. This calibration needs to be performed at a minimum of once every 3-4 years to ensure acceptable quality control as per treatment site SOPs.

**Treatment Dose Interruptions**

Treatment dose interruption for the single fraction Gy regimen is not applicable.

For a patient who will be receiving 20/25 Gy over 5 fractions, dose interruption must occur if a patient experiences a Grade 3 or higher adverse reaction in any organ/tissue that is due to the radiation therapy. The fractionated therapy can only resume once the adverse reaction has recovered or stabilized back to Grade 2 or less.

Patients with tumors involving the central nervous system are excluded from this study. It is anticipated that over 50% of patients recruited into this study will require symptomatic low-dose EBRT to bony metastases, with involvement of other soft tissue organ lesions for the rest of the patients.

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## 10.11 Appendix 11: Country-Specific Requirements

<To be adjusted per country requirements>

## 10.12 Appendix 12: Abbreviations and Trademarks

| | |
|---|---|
| ADL | Activities of daily life |
| ADT | Androgen deprivation therapy |
| AE | Adverse event |
| Akt | Antiapoptotic kinase B |
| ALT | Alanine aminotransferase |
| Anti-HBc | Hepatitis B core antibody |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| $AUC_{(0-6)}$ | AUC from time zero (predose) to 6 hours postdose |
| $AUC_{(0-12)}$ | AUC from time zero (predose) to 12 hours postdose |
| $AUC_{(0-inf)}$ | AUC from time zero (predose) extrapolated to infinity |
| $AUC_{(0-t)}$ | AUC from time zero (predose) to time of last quantifiable concentration |
| BC | Breast cancer |
| BID | Twice daily |
| BP | Blood pressure |
| BPI-SF | Brief Pain Inventory – Short Form |
| BUN | Blood urea nitrogen |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed concentration |
| $C_{min}$ | Minimum observed concentration |
| COVID-19 | Coronavirus disease 2019 |
| $CO_2$ | Carbon dioxide |
| CR | Complete response |
| CRO | Clinical Research Organization |
| CT | Computerized tomography |
| ctDNA | Circulatory tumor deoxyribonucleic acid |
| CYP | Cytochrome P450 |
| DCR | Disease control rate |
| DLT | Dose-limiting toxicity |
| DMC | Data Monitoring Committee |
| EBRT | External beam radiotherapy |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |

| | |
|---|---|
| eCRF | Electronic case report form |
| ED | Early Discontinuation |
| EDC | Electronic data capture |
| ENOX | Ecto-NOX disulfide-thiol exchanger |
| EORTC-QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients |
| EOT | End of Treatment |
| FACT-P | Functional Assessment of Cancer Therapy - Prostate |
| FAS | Full Analysis Set |
| FSH | Follicle-stimulating hormone |
| FU | Follow-up |
| GCP | Good Clinical Practice |
| Gy | Gray |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HRT | Hormone replacement therapy |
| IB | Investigator's Brochure |
| $IC_{50}$ | Half maximal inhibitory concentration |
| ICF | Informed consent form |
| ICH | International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| LDH | Lactate dehydrogenase |
| LuPSMA-617 | $_{177}$lutetium prostate-specific membrane antigen |
| MCH | Mean corpuscular hemoglobin |
| MCV | Mean corpuscular volume |
| mCRPC | Metastatic castration-resistant prostate cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| n | Number of patients/events |

| | |
|---|---|
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Events |
| NCSLC | Non-small-cell lung cancer |
| ORR | Objective response rate |
| OS | Overall survival |
| PCWG-3 | Prostate Cancer Working Group 3 |
| PD | Pharmacodynamic(s) |
| PEQ | Patient Experience Questionnaire |
| PFS | Progression-free survival |
| P-gp | P-glycoprotein |
| PI3 | Phosphoinositide 3-kinase |
| PK | Pharmacokinetic(s) |
| PPS | Per protocol Set |
| PR | Partial response |
| PRO | Patient Reported Outcome |
| PSA | Prostate-specific antigen |
| PSMA | Prostate-specific membrane antigen |
| QA | Quality assurance |
| QC | Quality control |
| QoL | Quality of life |
| QTc | Corrected QT interval |
| QTcF | Corrected QT interval using Fridericia's formula |
| RBC | Red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | Recommended Phase 2 dose |
| RT-PCR | Reverse transcription polymerase chain reaction |
| S1P | Sphingosine-1-phosphate |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SAS | Statistical Analysis Software |
| SD | Stable disease |
| SoA | Schedule of Activities |
| SOC | Standard of care |
| SOP | Standard operating procedure |
| SRE | Skeletal-related events |

| | |
|---|---|
| SSC | Safety Steering Committee |
| SSE | Symptomatic skeletal events |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal phase half-life |
| TEAE | Treatment-emergent adverse event |
| $T_{max}$ | Time to first occurrence of $C_{max}$ |
| TMEP | Transmembrane electron potential |
| UGT | Uridine 5'-diphospho-glucuronosyltransferase |
| ULN | Upper limit of normal |
| US | United States |
| WBC | White blood cell |
| WOCBP | Woman of childbearing potential |

# 11 References

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# Investigator Agreement Page

**Declaration of the Principal or Global Coordinating Investigator**

<This page should be used for studies with EU sites but is not mandatory for US studies.>

**Title**: A Phase 1b/2a Multicenter Study of NOX66 and External Beam Radiotherapy in Patients with Metastatic Castration-resistant Prostate Cancer and Other Solid Tumors

This study protocol (Version 3.0, dated 21 Jan 2022) was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the study drug as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 1996 and the guidelines on Good Clinical Practice.

**Principal or Global Coordinating Investigator**

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

**Declaration of the National Coordinating Investigator** *<country-specific, please adjust as required>*

**Title:** A Phase 1b/2a Multicenter Study of NOX66 and External Beam Radiotherapy in Patients with Metastatic Castration-resistant Prostate Cancer and Other Solid Tumors

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**National Coordinating Investigator**

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

**Declaration of the Investigator**

**Title**: A Phase 1b/2a Multicenter Study of NOX66 and External Beam Radiotherapy in Patients with Metastatic Castration-resistant Prostate Cancer and Other Solid Tumors

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol (Version 3.0, dated 21 Jan 2022), Investigator's Brochure, EDC system/electronic CRF (eCRF) and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the Local Study Center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number