CLINICAL STUDY PROTOCOL

Title: NOX66 and Palliative Radiotherapy in Patients with Late-Stage Prostate Cancer – a Phase 1b Proof of Concept and Dose confirmation study.

Protocol Number: NOX66-002A

Development Phase: 1b

Product: NOX66 (Idronoxil Suppository Formulation)

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Version: 5.1

Date: 11 July 2019

SIGNATURES

SPONSOR

This document has been approved in accordance to Noxopharm Limited's current policies and procedures

Dr.Greg van Wyk Chief Executive Officer & Chief Medical Officer Noxopharm Limited	**Date**

INVESTIGATOR

I confirm that I have read and understood the protocol and I agree to meet all the obligations and restrictions outlined therein. All information regarding this protocol and the investigational product(s) will be treated as strictly confidential. I agree to conduct the study in all respects in accordance with the study protocol and the ethical principle of the current amendment of the declaration of Helsinki and with ICH GCP.

_____	_____
Signature of Principal Investigator	**Date**
_____	_____
Printed Name of Principal Investigator	**Institution Name**

PROTOCOL SYNOPSIS

Name of Company Sponsor	NOXOPHARM LIMITED
Title of Study	NOX66 and Palliative Radiotherapy in Patients with Late-Stage Prostate Cancer – a Phase 1b Proof of Concept and dose confirmatory study.
Study Number	NOX66-002A
Development phase	Phase Ib
Name of Active Ingredient	Idronoxil
Description of Investigational product	NOX66 is idronoxil in a hydrogenated lipophilic base formulated as a suppository, designed to protect idronoxil from Phase 2 metabolism.
Mode of Administration and dosage	NOX66 will be self-administered as a rectal suppository. Patients will be instructed in the procedure of suppository administration Dosage is 1, 2 or 3 suppositories (idronoxil dosage 400mg, 800mg or 1200mg) for 13 (+3) consecutive days.
Number of subjects planned	Up to 24 patients in 3 idronoxil dose level cohorts of 4 patients (n=12) and an expansion cohort of 12 patients.
Indication / Patient Population	Metastatic castrate-resistant prostate cancer with no remaining standard treatment options. Patients must have at least one metastatic lesion which is amenable to RT.
Study period and duration of treatment	The study will comprise two parts: 1. Treatment and follow up (24 weeks) comprising: • NOX66 (Day 1-16) • Palliative Dose Radiation therapy (Day 2-9) • 6-week follow up • 12-week follow up • 24-week follow up 2. Long term follow-up: • Ongoing follow up and monitoring of patient to assess long term effects of NOX66 administration and survival including scheduled follow up at 9 ,12, 15, 18, 21 & 24 months from treatment commencement date.
Primary study objective	• To determine the tolerability and toxicity of NOX66 administered in conjunction with palliative radiation therapy
Secondary study objectives	• To observe any clinical response to treatment of NOX66 in combination with palliative radiation therapy • To observe the effects of NOX66 use on long term (24 months) outcomes for patients

	• To document Progression Free Survival (PFS) and Overall Survival (OS) of patients • Exploratory: to measure levels of idronoxil
Methodology	Patients will have a minimum of one (1) lesion which is amenable to radiation therapy and be treated in combination with idronoxil (NOX66). The Study will involve 13-16 days of treatment with NOX66 and radiation therapy as follows: • Baseline: Tumour assessment scan using CT/MRI, screening laboratory assessments (including PSA levels), and pain assessment (Brief pain Inventory-Short Form) • Day 1-16: NOX66 will be administered rectally (one, two or three suppositories daily, depending on cohort allocation) • Day 2-9: Lesions selected for irradiation will receive palliative dose (20Gy) radiation therapy in 5 fractionated doses over 7 days. • Week 6: Initial follow up scan using CT/MRI, follow up laboratory assessments (including PSA levels), and pain assessment • Week 12: Second follow up scan using CT/MRI, follow up laboratory assessments (including PSA levels), and pain assessment • Week 24: third follow up scan using CT/MRI, follow up laboratory assessments (including PSA levels), and pain assessment • Month 9 (3 months after Week 24): Performance Status (ECOG), scan using CT/MRI/US, PSA measure and pain assessment. • Month 12: Performance Status ECOG), scan using CT/MRI, PSA measure and pain assessment. • Month 15, 18, 21 & 24 (every 3 months after Month 12 follow up visit for another 12 months): Scan using CT/MRI/US & PSA measure. Patients will continue to be followed up after 24 months at the discretion of the investigator. The study steering committee (SSC) will review emerging safety data and determine the dose cohort escalation following end of treatment cycle of final patient in a cohort. Following interim analyses of safety data and tumour response at WEEK 6 of 3 dose cohorts of 12 total patients, the SSC will inform on dose for cohort expansion of additional 12 patients. Baseline CT/MRI scans shall be assessed and any lesions which can be measured in accordance with RECIST criteria will be noted as “target lesions”. Target measurable lesions may either be at the site of irradiation or non-irradiated. Patients with identified measurable target lesions will be assessed for objective response using RECISTv1.1 criteria. All patients will have radiological scans, PSA, ECOG and pain scores assessed for clinical response by a Radiation Oncology Expert Committee.
Criteria for Evaluation	**Safety:** assessed through the analysis of routine clinical and laboratory assessments of haematology and chemistry parameters, physical

	examinations and vital signs. Adverse event monitoring will be performed and assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE) scoring system. **Efficacy:** Overall response will be assessed by a Radiation Oncology Expert Committee based on change from baseline of tumours on imaging data by RECISTv1.1 criteria for measurable lesions, total pain score, PSA and ECOG score. **Biomarkers**: Serum levels of PSA will be measured at baseline and four-time points (end of Treatment Cycle (Day 16), at Week 6 ,12 and 24 post therapy. Plasma levels of idronoxil will be measured at baseline and two post therapy time points, end of Treatment Cycle (Day 16) and at Week 6.
Statistical methods	No statistical analysis of results will be conducted due to the size of the cohort. Primary endpoint will be reported as the number of patients experiencing toxicity >2 and dose limiting toxicities (DLT) with description of the toxicity. Secondary endpoints will be reported as the response (measured and observed) to treatment of each patient over the 24-week initial period. Data will be presented in table form, with adverse events and outcomes listed per patient. Overall and progression-free survival, PSA and pain scores collected during the extended follow-up period will be summarized in the same manner as for the immediate post-treatment follow-up period. A detailed Statistical Analysis Plan will be developed and approved prior to data lock.
Inclusion criteria	1. Provision of informed consent. 2. ≥ 18 years of age. 3. Histologically confirmed prostate cancer and/or PSA of >100 ng/mL at original diagnosis. 4. Metastatic disease evidenced by either CT/MRI imaging or bone scan. 5. Objective evidence of disease progression as defined by either: i. Radiographic progression of in nodal or visceral metastases and bone disease progression with 2 or more new lesions ii. Rising PSA value ≥2ng/ml in at least 3 measurements, at least 1 week apart, with castrate levels of serum testosterone. 6. Eligible to receive palliative radiation therapy to at least one symptomatic lesion for management of disease. 7. ECOG Performance status 0-2. 8. A minimum life expectancy of 24 weeks. 9. Adequate bone marrow, hepatic and renal function as evidenced by: • Absolute neutrophil count (ANC) > 1.5 x 10^9/L • Platelet count > 100 x 10^9/L • Hemoglobin > 9.0 g/dL • Serum bilirubin < 1.5 x ULN

	• AST/ALT (SGOT/SGPT) < 2.5 x ULN for the reference laboratory or < 5 x ULN in the presence of liver metastases • Serum creatinine < 1.5 x ULN 10. Ongoing androgen deprivation therapy with luteinizing hormone-releasing hormone (LHRH) agonist or antagonist. 11. At least 4 weeks must have elapsed prior to commencement of NOX66 treatment since prior chemotherapy, investigational drug or biologic therapy and any toxicity associated with these treatments has recovered to ≤ NCI-CTCAE (version 4.03) Grade 1. 12. At least 21 days must have elapsed following major surgery and any surgical incision should be completely healed.
Exclusion criteria	1. Tumour involvement of the central nervous system. 2. Uncontrolled infection or systemic disease. 3. Clinically significant cardiac disease not well controlled with medication (e.g. congestive heart failure, symptomatic coronary artery disease, angina, and cardiac arrhythmias) or myocardial infarction within the last 12 months. • Patients with a QTc > 470 msec on screening ECG 4. Concurrent systemic chemotherapy or biological therapy. 5. Any situation where the use of suppository therapy is contra-indicated or impractical (e.g. chronic diarrhoea, colostomy, ulcerative colitis). 6. Known human immunodeficiency virus (HIV) or Hepatitis B or C (active, previously treated or both). 7. Any subject whose testosterone is not suppressed i.e. is > 0.5nmols/L. 8. Any other reason which, in the opinion of the investigator, will preclude suitable participation in the study.

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2 LIST OF ABBREVIATIONS

Abbreviation/term	Definition
AE	Adverse Event
Akt	Protein kinase B
ALP	Alkaline Phosphatase
ALT/SGT	Alanine Transaminase / Serum Glutamate pyruvate Transaminase
AST/SGOT	Aspartate aminotransferase/ Serum Glutamate Oxaloacetate Transaminas
β-hCG	Beta-human Chorionic Gonadotropin
BPI-SF	Breif Pain Inventory- Short Form
^{0}C	Degrees Celsius
CBC	Complete blood count (otherwise known as FBC)
c-FLIP	Cellular FLICE [FADD-like IL-1b-converting enzyme]-inhibitory protein
CFR	Code of Federal Regulations
CRF/eCRF	Case report form/electronic Case report form
CR	Complete Response
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CT	Computerised Tomography
dL	Deciliter
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ENOX	External Membrane NADH oxidase
ENOX1	ENOX Type 1 - Constitutive NADH oxidase
ENOX2	ENOX Type 2 - Tumour-associated NADH oxidase
FDA	Food and Drug Administration
g	Gram(s)
Gy	Gray
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH GCP	International Conference on Harmonization Good Clinical Practice
ICRU	International Commission on Radiation Units
IV	Intravenous
kg	Kilogram
LD	Longest Diameter
LHRH	Luteinizing hormone-Releasing Hormone
µ	Micro
µM	Micromolar

MDR	Multidrug Resistance
mg	Milligram(s)
mL	Milliliter(s)
min	Minute(s)
msec	Millisecond
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro Ribose Nucleic Acid
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NAD(H)	Nicotinamide Adenine Dinucleotide
NCI CTC	National Cancer Institute, Common Toxicity Criteria
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural Killer cells
OS	Overall Survival
PCWG3	Prostate Cancer Working Group 3
PD	Progressive Disease
PET	Positron Emission Tomography
PI	Principal Investigator
PI3K/Akt	Phosphoinositide 3-kinase /protein Kinase B
PFS	Progression Free Survival
PMSA	Prostate Membrane Specific Antigen
PSA	Prostate Specific Antigen
PR	Partial Response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
ROEC	Radiation Oncology Expert Committee
RT	Radiation therapy
S1P	Sphingosine-1-phosphate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SSC	Study Steering Committee
SOC	System Organ Class
TGA	Therapeutic Goods Administration
ULN	Upper Limit of Normal
US	Ultrasound
XIAP	X-linked inhibitor of Apoptosis Protein

3 ROLES AND RESPONSIBILITIES

3.1 SPONSOR

Noxopharm Limited will conduct the study in all respects in accordance with the ethical principle of the current amendment of the Declaration of Helsinki and with ICH GCP regarding responsibilities of the Sponsor. Noxopharm Limited reserves the right to terminate the study at any time. A written explanation will be provided to the Investigator should the study be terminated. The Investigator is responsible to inform the HREC of such a decision and to return all study materials to the Sponsor.

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3.2 CONTRACT RESESARCH ORGANISATION

Activities relating to the conduct and management of this trial may be delegated to Contract Research Organizations. All activities will be conducted in accordance with ICH GCP, with the overall responsibility for the study remaining with the Sponsor.

3.3 INVESTIGATOR AND SITES

This study will be conducted at oncology clinics across Australia, Georgia and New Zealand. Sites will be approved for participation by the applicable HREC, local and national authorities. By signing this protocol on behalf of his / her research institute, the Principal Investigator has agreed to undertake the responsibilities of conducting this clinical research study.

3.4 MEDICAL OVERSIGHT

Medical management and patient care while participating in this study is the responsibility of the Principal Investigator. Review of adverse events and decisions on continuation in trial, medical intervention and other related activities for an individual patient shall be at the discretion of the Principal Investigator. Review of adverse events and decisions on continuation in trial, medical intervention and other related activities for the overall study shall be at the discretion of the Study Steering Committee – consisting of Principal Investigators, an independent Oncologist and a representative of the Sponsor company.

4 INTRODUCTION

The mainstays of oncology therapy – chemotherapy and radiation therapy – provide varying degrees of efficacy in patients with cancer, and for those with late stage metastatic disease the prognosis for patients can be very poor. A primary reason for these poor outcomes is the presence of chemo- and radio-resistance mechanisms in tumour cells.[1] This resistance leads to higher doses of chemotherapy and/or radiation therapy being required, to a point where the adverse effects (toxicity) of therapy outweighing the benefits, or that treatment no longer provides any benefit for patients. Finding a treatment that can overcome some or all of these resistance mechanisms may lead to:

- Providing therapy with clinically meaningful outcomes for patients with end stage and late stage cancers
- Improving clinical outcomes for patients undergoing established chemotherapy and radiation therapy treatment
- Allowing lower doses of chemotherapy and radiation therapy to be used in future treatment of patients, providing similar efficacy outcomes while minimizing toxicity – providing treatment for patients who may otherwise not receive treatment (e.g. frail and elderly patients)

This study will investigate the use of NOX66 - idronoxil formulated in a lipophilic base – in combination with palliative radiation therapy, in patients with end stage castrate resistant prostate cancer. The data generated, in conjunction with other early phase studies, will be used to inform the development of larger studies to investigate the efficacy and safety of NOX66 (idronoxil) in combination with radiation therapy and chemotherapy.

The key hypotheses to be tested in this study are:

a. That idronoxil can be safely added to palliative dose radiation therapy.
b. That idronoxil, via its selective inhibition of PI3K/Akt signalling in tumour cells, may sensitise tumours to palliative doses of radiation therapy, with efficacy signals being seen in this study.
c. That any efficacy seen in irradiated tumours may lead to an effect on non-irradiated tumours.

Furthermore, this study will investigate three doses of NOX66 to determine if there is any difference in safety and / or efficacy signals with increasing dose and to determine the optimal dose for future radiation therapy combination studies.

4.1 MULTI-DRUG RESISTANCE, CHEMO- AND RADIO-SENSITISATION AND IDRONOXIL

Tumour cells develop a variety of mechanisms to avoid the effects of anti-cancer drugs. The term multi-drug resistance (MDR) refers to the typical situation where resistance to

treatment extends to most, if not all, chemotherapy drugs and treatment regimens. Some tumour cells display MDR from the outset (inherent resistance), while others develop it following exposure to chemotherapy (acquired resistance). Both forms of resistance are based on the same MDR mechanisms.

A range of mechanisms are involved in MDR including: altered membrane transport, enhanced DNA repair, alteration of target proteins, activation of alternate signalling pathways, enzymatic digestion of drug, blockage of apoptosis, up-regulation of tumour-promoter genes and down-regulation of tumour-suppressor genes.[1-4] Of these, enhanced DNA repair also is an important mechanism in the resistance of tumour cells to radiation therapy.[5,6]

Linking these various functions are a small number of upstream pro-survival pathways, particularly those regulated by phosphoinositide 3-kinase (PI3K), the serine/threonine kinase Akt, and the anti-apoptotic pathway NF-kB, all of which are over-expressed in many forms of cancer.[6,7]

The key role of the PI3K/Akt/NF-kB signalling pathways in chemo- and radio-resistance mechanisms has marked them as key targets for drug development. These pathways, however, have an essential role in the survival of all cells, cancerous or otherwise[6] - a fundamental that has blocked the successful development of any drug to target this pathway and provide selective targeting of cancer cells. The mechanism of action of idronoxil may overcome this barrier.

Idronoxil is a small molecule synthetic derivative of the naturally-occurring isoflavone, genistein. Genistein has been shown to sensitise a range of solid cancer cells to both chemotherapy and radiation therapy, via both direct inhibitory effects on signal transduction and indirectly by genomic effects.[8-11] Idronoxil has been specifically developed to enhance the anti-cancer properties observed with genistein by reducing the level of Phase 1 metabolism (and consequent loss of bio-activity) – leading to activity 10-30 times greater.[12]

The mechanism of action of idronoxil means that it can selectively inhibit cancer cell PI3K/Akt pathways without affecting non-cancer cells. It does this by targeting an upstream regulator of PI3K/Akt which is expressed differently in cancer cells. Inhibition by idronoxil of this upstream target deprives the tumour cell of its key pro-survival signalling pathways, leading to down-regulation of PI3K/Akt.

4.2 IDRONOXIL – A SELECTIVE INHIBITOR OF PI3K/AKT

Idronoxil, also known as phenoxodiol, is a first-in-class, selective PI3K/Akt inhibitor. Details of the pharmacology of idronoxil are found the current version of the NOX66 Investigator's Brochure.

The primary target of idronoxil is external membrane NADH oxidase Type 2 (ENOX2). ENOX enzymes are located on the external membrane of cells and by regulating the movement of

electrons (protons) across the plasma membrane are responsible for maintaining the transmembrane electron potential.[13]

Human cells have the capacity to express two forms of ENOX known as ENOX1 and its splice variant, ENOX2. ENOX1 is the constitutive form expressed by healthy cells while current literature suggests that ENOX2 is the active form of the ENOX enzyme in all cancer cells. Idronoxil binds to the motif that distinguishes ENOX2 from ENOX1, but has no binding affinity to ENOX1.[14]

Inhibition of ENOX2 leads to an accumulation of protons within the plasma membrane of the cancer cell, creating a cascade of events involving the inhibition of a variety of downstream pro-survival pathways as described in Section 5.3. Because idronoxil selectively binds to ENOX2, with no binding affinity for ENOX1, only the cells expressing ENOX2 (i.e. tumour cells) are affected by idronoxil.[15]

4.3 IDRONOXIL – SUMMARY OF MECHANISM OF ACTION

The mechanism of action of idronoxil is summarized below, in Figure 1.

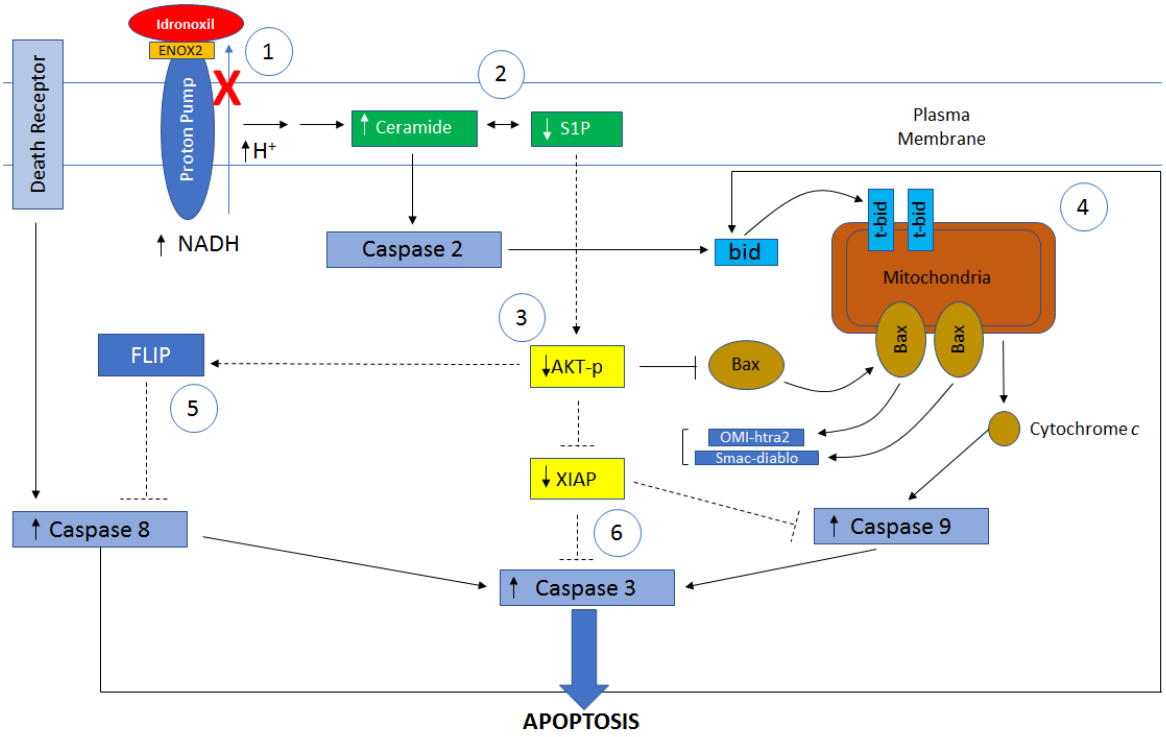


Figure 1 Sequence of biochemical events following binding of idronoxil to ENOX2.

The cascade of events is as follows:[13-16]

1. Idronoxil binds to ENOX2, leading to inhibition of the trans membrane electron pump which, in turn, leads to an accumulation of proton ions within the plasma membrane.

2. Accumulation of protons disrupts sphingomyelin pathway with blockage of ceramide conversion to sphingosine-1-phosphate (S1P) – leading to a decrease in S1P and an increase in Ceramide within the plasma membrane.
3. Decrease of S1P leads to a reduction in PI3K, AKT and XIAP and an increase in Caspase 2.
4. Reduction in AKT leads to reduction in NF-kB and allows up regulation of the intrinsic (mitochondrial) pathway of apoptosis, via an increase in Caspase 9 and Caspase 3, leading to cell death.
5. Reduction in AKT also results in an inhibition of FLIP resulting in an increase in Caspase 8 (activated via the Death Receptor on the Protein Membrane) – leading directly and indirectly (via the intrinsic pathway) to an increase in Caspase 3 and apoptosis.
6. Reduction in XIAP prevents down regulation of Caspase 9 and Caspase 3, supporting apoptosis.

Both *in vitro* and *in vivo*, idronoxil provides high levels of synergistic cytotoxicity with a wide range of chemotoxic (cisplatin, carboplatin, paclitaxel, gemcitabine, doxorubicin) and chemostatic (topotecan) drugs across a broad range of cancer phenotypes.[17-19]

Where the terms chemo-sensitisation and radio-sensitisation often are used in the sense of priming cells to undergo greater drug- or radiation-induced damage, idronoxil (as used in this study) acts to block the ability of tumour cells to repair and recover from damage caused by chemotherapy and radiation therapy.

4.4 IDRONOXIL – INTRAVENOUS AND ORAL DOSAGE FORMULATION

Following pre-clinical development, Idronoxil commenced a clinical development program in 2000, for intravenous (IV) and oral administration. Between 2000 and 2009 a series of phase 1 and phase 2 studies were conducted, with a multi-centre Phase 3 trial commenced to investigate oral idronoxil as a chemo-sensitiser of carboplatin in late-stage, chemo-refractory ovarian cancer cases.[20] Over 400 patients with late-stage cancer were treated in Phase 1, 2 and 3 clinical studies.[21] The clinical development program was stopped during the phase 3 program due to slow recruitment into the pivotal trial and no difference in efficacy between the treatment arms. Further information regarding previous studies is contained in the current NOX66 Investigator's Brochure.

4.5 IDRONOXIL – NOX66 DOSAGE FORMULATION

The lack of efficacy observed in the Phase 2 and 3 trials of oral idronoxil with carboplatin has been attributed to a high level (> 99%) of metabolism. Idronoxil undergoes Phase 2 metabolism within the body, whereby water-insoluble compounds are converted into more

water-soluble forms through the action of transferase enzymes (present in gut mucosa and liver). This is achieved by attaching a glucuronide or sulphate chemical group. The resulting water-soluble drug conjugate is biologically inactive, with reactivation requiring enzymatic digestion by glucuronidases and sulphatases present in the lysosomes of target cells. Many phenolic drugs undergo this process including aspirin, codeine, paracetamol, naloxone, propofol and steroid hormones.

Most normal cells contain high levels of glucuronidases and sulphatases, accounting for the biological activity of other phenolic drugs. Recent studies, however, suggest that cancer cells amend or inhibit this function as one of their multi-drug resistance mechanisms. Breast cancer cells, for example, have been found to contain negligible levels of deconjugating enzymes,[22] while some other forms of cancer undertake their own Phase 2 (transferase) metabolism.[23]

NOX66 is a suppository dosage form of idronoxil, formulated in a hydrogenated lipophilic base and developed specifically to reduce the exposure of the drug to Phase 2 metabolism. Rectal absorption is a standard method of drug administration where Phase 2 metabolism is sought to be minimized, with venous drainage from the distal part of the rectum feeding into the inferior vena cava, thereby avoiding first pass liver metabolism. The lining of the rectum also is largely devoid of transferase activity.[24-26]

Rat studies conducted by Noxopharm[27] have suggested that when administered rectally in the form of NOX66:

- idronoxil is readily bioavailable
- the degree of Phase 2 metabolism is reduced
- the drug readily distributes within tissues
- is excreted primarily via the urine
- administered drug is largely eliminated within 24 hrs, with no evidence of accumulation.

4.6 NOX66 – CURRENT DRUG DEVELOPMENT PROGRAM

This study forms part of a program of phase 1 studies designed to provide insight in to the safety and signals for efficacy of NOX66 in various cancer therapy settings, namely:

- Safety and PK of NOX66 as monotherapy
- NOX66 in combination with chemotherapy alone
- NOX66 in combination with palliative radiation therapy alone, and the effects on tumours externally targeted with radiation
- NOX66 in combination with palliative radiation therapy alone, and the effects on tumours not targeted with radiation therapy
- NOX66 in combination with radiation therapy alone, with radiation therapy being administered as brachytherapy (internal targeting of treatment)
- NOX66 in combination with chemotherapy and palliative radiation therapy

5 STUDY RATIONALE

5.1 RATIONALE FOR COMBINATION WITH RADIATION THERAPY

5.1.1 Radio-sensitisation

Many cancer patients receive radiation therapy, either as part of a treatment regimen or in the palliative setting, to reduce tumour size and manage pain and symptoms associated with end stage cancer.[28]

The anti-cancer effect of ionizing radiation relates to its ability to cause double strand breaks in DNA, and the non-specificity of this effect means that the dosage of radiation able to be applied is self-limiting. This dosage limitation is exacerbated by the presence of factors (radio-resistance) that render some cancer cells less sensitive to the damaging effects of ionizing radiation, while normal cells are without those same factors and retain full radio-sensitivity, as discussed in Section 5.1.

The use of NOX66 as a tumour cell-specific sensitiser of radiation therapy may provide greater response to targeted radiation therapy within the tumour cells, with the tumour specific nature of NOX66 activity leading to no greater effect on non-tumour cells. As such, NOX66 is expected to increase the response to palliative dose radiation therapy, reducing target tumour size beyond those expected with palliative radiation therapy alone, with no significant increase in serious and severe adverse events.

5.1.2 Abscopal Response

An abscopal (from Latin ab-scopus, away from the target) response describes tumour regression at sites distant to an irradiated field, and is a rare event seen in patients with various types of metastatic tumours receiving palliative radiation therapy to a single metastasis. First described[29] over 50 years ago, the response is sufficiently rare to warrant clinical reports of individual cases, with responses in melanoma, lung cancer, kidney cancer and cutaneous lymphomas variously reported.[30-33]

In the only prospective clinical study[34] reported to date, 41 patients with metastatic solid cancers were treated with a combination of standard cytotoxic chemotherapy, external beam RT, and granulocyte-macrophage colony stimulating factor (GM-CSF). A maximum 2 lesions were irradiated (35 Gy in 10 fractionated doses) and the response measured by CT scan in both irradiated and non-irradiated lesions. An abscopal response was reported in 11/41 (27%) patients (4 lung cancer, 5 breast cancer, 2 thymic cancer). Two of these cases had a complete response (lung cancer) and 9 had a partial response. The median overall survival was 21 months for abscopal responders versus 8 months for the non-responders.

While the mechanism underlying this phenomenon is unknown, the results of the above study, in conjunction with a range of pre-clinical studies, points to the involvement of soluble signalling factors including tumour antigens that are hypothesized to be released by the dying irradiated tumour cells to mediate an immune response against non-irradiated lesions.[35,36,37]

In addition to its anti-cancer effects, idronoxil also has confirmed immune-stimulatory effects.[38] Human peripheral blood CD56+ natural killer (NK) cells show increased lytic activity against K562 (myelogenous leukaemia cell line) in the presence of idronoxil. Also, in a mouse colon cancer (CT-26) model in which idronoxil monotherapy produced a significant anti-cancer effect, ex vivo studies showed that idronoxil activated both NK and tumour-specific tumour cell lysis. As such, it is hypothesized that NOX66 may produce an abscopal effect in treating non-irradiated lesions when combined with radiation therapy.

In this study, we will also monitor for any changes in non-irradiated lesions, to determine if NOX66 may induce an abscopal response when combined with radiation therapy.

5.2 RATIONALE FOR DOSE OF NOX66

Pre-clinical studies in mice consistently found an effective chemo-sensitising (standard cytotoxic drugs) dose of idronoxil to be between 100-150 mg/kg.[12] Phase 2 metabolism in these models was observed to be significant, with 10-30% of idronoxil remaining as free drug and the remainder being excreted as the conjugated (inactive) metabolites. As such, an effective dose in rats of 20mg/kg free idronoxil has been used. This converts to an equivalent human dose of 3-4mg/kg, based on body surface area. Dosing in line with this was used for the intravenous and oral dosage formulations of idronoxil, with a dose of 1200mg being used for the Phase 3 oral study (Refer to Investigators' Brochure for further information)

Whilst the oral dose of idronoxil was found to be ineffective to due Phase 2 metabolism, these studies do show that idronoxil has minimal effect on non-tumour cells (in which deconjugation does occur and therefore the cells are exposed to active idronoxil). As such, doses in line with the oral dosing regimen have been selected for this and other phase 1 studies. NOX66 has been developed to protect idronoxil from complete Phase 2 metabolism, enabling the active ingredient to target tumour cells and, in the case of this study, sensitise the target tumours to radiation therapy.

While idronoxil displays significant anti-cancer effect in animals as a monotherapy,[12,39] the applicants believe that its potential clinical use lies in its sensitizing abilities, which requires having the drug present in the tumour cell during the period of induction of the cytotoxic damage and the repairing process of that damage.

5.3 POTENTIAL RISKS

As with all products and formulations in Phase 1 development, the adverse event profile of idronoxil in the formulation of NOX66 has not been fully established.

In vitro studies have shown no binding affinity for idronoxil to healthy human cells and, as such, minimal adverse events directly due to idronoxil are expected. This has been supported

by the clinical research program of IV and oral formulations of idronoxil, where no adverse events of toxicity Grade 2 or higher have been reported.

It is expected that any adverse events observed in the study will be due to the use of the combination of NOX66 with palliative radiation therapy. Any adverse events greater than normally observed with this therapy in the patient group for this study (e.g. fatigue at level greater than Grade 2) are expected to be related to a greater efficacy of the treatment (due to the sensitizing effect of NOX66).

5.4 POTENTIAL BENEFITS

As a Phase 1 sighting Study, the efficacy (benefits) of combining palliative radiation therapy and idronoxil (NOX66) is not known. The hypothesis, however, is that the effect of idronoxil in sensitizing the cancer cells to radiation therapy will provide an enhanced response to this treatment, with a clinical response observed in the patients participating in the trial.

6 STUDY OBJECTIVES AND HYPOTHESES

6.1 PRIMARY OBJECTIVE

- To determine the safety and tolerance of idronoxil, administered as the NOX66 formulation in escalating dose cohorts and concurrently with palliative radiation therapy, in patients with end stage castrate resistant prostate cancer.

6.2 SECONDARY OBJECTIVES

- To investigate whether idronoxil administered as the NOX66 formulation will sensitise end stage prostate cancer to palliative radiation therapy and provide a clinically relevant response to treatment according to:
    - RECISTv1.1 criteria for measurable lesions, within irradiated and non-irradiated target lesions
    - Improvement in total pain scores using BPI-SF instrument
    - To observe changes in serum PSA
    - Review of CT/MRI scans by Radiation Oncology Expert Committee –assessment of observable and or symptomatic changes from baseline over time

- To determine a dose of NOX66 to continue into late phase clinical trials
- To investigate plasma idronoxil levels following NOX66 therapy
- To determine Progression Free Survival (PFS) and Overall Survival (OS)

7 STUDY DESIGN

This is an open-label Phase Ib dose confirmation and proof of concept study in up to 24 patients with end stage castrate resistant prostate cancer who are being considered for or undergoing palliative radiation therapy for pain and symptom management. Patients will have a minimum of one (1) lesion which is amenable to radiation therapy. Palliative RT (20Gy over 5 fractions) will be delivered to selected lesion in combination with rectally administered idronoxil (NOX66).

This study is intended to provide information regarding the safety of this treatment combination and justification for a larger Phase 2/3 study in the treatment of patients with combination of NOX66 and palliative radiation therapy.

Clinical response to treatment will be assessed by radiological CT/MRI scans, where applicable objectively measures by RECISTv1.1, by pain response as evaluated by Brief Pain Inventory Short Form, ECOG scores and by monitoring PSA as surrogate marker with overall (observable and symptomatic) response based on data review by an independent Radiation Oncology Expert Committee (ROEC). Local response will be based on investigator review of data in conjunction with ROEC.

PSA will be monitored as a surrogate marker of response and pain response will be evaluated using the Brief Pain Inventory Short Form throughout the study.

Patients will be suitable for the study as they become eligible for, and will be given, palliative radiation therapy for management of their cancer.

Three dose cohorts will be investigated in this study with dosing based on criteria outlined in section 10.2.7. The three doses of idronoxil investigated include:

- 400mg idronoxil provided as one NOX66 suppository per day
- 800mg idronoxil provided as one NOX66 suppository twice daily
- 1200mg idronoxil provided as one NOX66 suppository three times daily.

Treatment will be for one cycle of combined radiation therapy and NOX66 with follow up assessments at Week 6, Week 12, Week 24 and every 3 months for the following 18 months. All patients will be followed up for disease progression and survival information either by retrospective review of medical records or by a physical visit or by telephone follow up call.

8 STUDY PARTICIPANTS

8.1 STUDY POPULATION

Twenty-four patients with metastatic castrate-resistant prostate cancer and scheduled to receive palliative radiation therapy for management of their disease will be enrolled into the study.

There will be no randomization or stratification in the study.

8.2 INCLUSION CRITERIA

Patients must fulfil all of the following inclusion criteria to be eligible to enrol into the study:

1. Provision of informed consent.
2. ≥ 18 years of age.
3. Histologically confirmed prostate cancer and/or PSA of > 100 ng/mL at original diagnosis
4. Metastatic disease evidenced by either CT/MRI imaging or bone scan.
5. Objective evidence of disease progression as defined by either:
    i. Radiographic progression of in nodal or visceral metastases and bone disease progression with 2 or more new lesions
    ii. Rising PSA value ≥2ng/ml in at least 3 measurements, at least 1 week apart, with castrate levels of serum testosterone.
6. Eligible to receive palliative radiation therapy to at least one symptomatic lesion for management of disease.
7. ECOG Performance status 0-2.
8. A minimum life expectancy of 24 weeks.
9. Adequate bone marrow, hepatic and renal function as evidenced by:
    - Absolute neutrophil count (ANC) > 1.5 x 10^9/L
    - Platelet count > 100 x 10^9/L
    - Hemoglobin > 9.0 g/dL
    - Serum bilirubin < 1.5 x ULN
    - AST/ALT (SGOT/SGPT) < 2.5 x ULN for the reference laboratory or < 5 x ULN in the presence of liver metastases
    - Serum creatinine < 1.5 x ULN
10. Ongoing androgen deprivation therapy with luteinizing hormone-releasing hormone (LHRH) agonist or antagonist.
11. At least 4 weeks must have elapsed prior to commencement of NOX66 treatment since prior chemotherapy, investigational drug or biologic therapy and any toxicity associated with these treatments has recovered to ≤ NCI-CTCAE (version 4.03) Grade 1.
12. At least 21 days must have elapsed following major surgery and any surgical incision should be completely healed.

8.3 EXCLUSION CRITERIA

Patients who have any of the following exclusion criteria are not eligible to participate in the study:

1. Tumour involvement of the central nervous system
2. Uncontrolled infection or systemic disease

3. Clinically significant cardiac disease not well controlled with medication (e.g. congestive heart failure, symptomatic coronary artery disease, angina, and cardiac arrhythmias) or myocardial infarction within the last 12 months
    - Patients with a QTc > 470 msec on screening ECG
4. Concurrent systemic chemotherapy or biological therapy
5. Any situation where the use of suppository therapy is contra-indicated or impractical (eg. chronic diarrhoea, colostomy, ulcerative colitis).
6. Known human immunodeficiency virus (HIV) or Hepatitis B or C (active, previously treated or both)
7. Any subject whose testosterone is not suppressed i.e. is > 0.5nmols/L.
8. Any other reason which, in the opinion of the investigator, will preclude suitable participation in the study.

8.4 SCREEN FAILURE AND STUDY WITHDRAWAL

Patients should begin protocol treatment within 2 weeks of enrolment at screening. Issues that would cause treatment delays longer than 2 weeks should be discussed with the Sponsor. If a patient does not proceed to receive protocol therapy following enrolment at screening, the patient's study enrolment will be cancelled, and the patient will be considered a screen failure. The Sponsor should be notified of screen failures as soon as possible.

Patients will be informed that they are free to withdraw from the study at any time and for any reason. Withdrawal criteria, other than progressive disease, can be defined as one or more of the following:

- an inter-concurrent illness that prevents further administration of idronoxil (NOX66) or radiation therapy;
- an adverse event to the combination treatment that is intolerable;
- the patient withdraws consent;
- the patient dies;
- general or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Investigator.

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records. The patient must be followed to establish whether the reason was an adverse event causally related to idronoxil (NOX66), and, if so, this must be reported in accordance with the requirements for adverse event reporting.

Patients will continue to be followed for the duration of the study, unless consent is withdrawn.

8.5 PATIENT REPLACEMENT

Patients who cannot be evaluated as part of the efficacy analysis may be replaced in the study at the discretion of the Sponsor.

9 STUDY MATERIALS

9.1 INVESTIGATIONAL STUDY PRODUCT

9.1.1 Description and Formulation

The active drug substance, idronoxil, is manufactured by chemical synthesis and is produced as a single monomer. Idronoxil is manufactured to > 98% purity.

Nomenclature

Codename: Idronoxil

Chemical Name: 2H-1-Benzopyran-7-0,1,3-(4-hydroxyphenyl)

Other names: Dehydroequol

Empirical Formula: $C_{15}H_{12}O_3$

Molecular Weight: 240.26 g/mol

NOX66 is idronoxil in a suppository dosage form for rectal delivery. The drug substance, idronoxil, is formulated in hydrogenated lipophilic base to yield suppositories with an approximate weight of 2.2 g and containing 400 mg drug substance.

9.1.2 Presentation, Storage and Handling

Presentation: NOX66 is presented as a solid dosage form as a suppository for rectal delivery.

NOX66 is presented in plastic sleeves in boxes. Each box contains 16 suppositories. Patients will be provided with 1, 2 or 3 boxes, depending on which cohort they are enrolled into.

NOX66 investigational product will be provided directly by the Sponsor to the clinical trials centres.

Storage and Handling: NOX66 boxes should be stored at the study centre in a secure area with limited access at 2-8°C (refrigerated) and protected from light. Any breach of investigational product storage conditions should be notified to the Sponsor on detection and the medication should be quarantined until the Sponsor authorizes usage or otherwise.

NOX66 is not expected to pose any safety risks to the Investigational staff under normal conditions of storage and distribution. Idronoxil has the lowest grade (Grade 4) of hazard classification (according to Regulation (EC) No. 1272/2008 [EU-GHS/CLP) with an acute oral

toxicity of between 300 to >2000 mg/kg body weight. The product also is contained within air-tight plastic moulding.

9.1.3 Labelling

Each box will be labelled with:

- the name of the Sponsor and address;
- the study protocol number;
- pharmaceutical dosage form, quantity of dosage units;
- name and strength of the product;
- the batch/lot number of the contents;
- period of use (expiry date or re-test date as applicable) in month/year;
- Caution Statement: "Caution: Clinical Trial Use Only; Keep out of reach of children.";
- storage instructions;
- PI name;
- Patient ID.

Each suppository will be labelled with:

- the name of Sponsor;
- the study protocol number;
- pharmaceutical dosage form, quantity of dosage units;
- name and strength of the product;
- the batch/lot number of the contents.

Boxes (plus any remaining contents) are to be accounted for.

9.1.4 Procurement and Distribution

NOX66 investigational product will be provided directly by the Sponsor.

Patients are to be given their NOX66 treatment following confirmation of eligibility (screening) and the scheduled commencement of treatment.

Patients to return medication following completion of NOX66 therapy for drug accountability.

9.2 INVESTIGATIONAL PRODUCT ADMINISTRATION

Idronoxil in the form of a suppository (NOX66) will be self-administered once, twice or three times daily depending on the patient cohort allocation and continue for up to 16 days.

Dosing will commence on the day prior to RT, continue daily during RT (including days in which RT is not given) and 7 days post RT completion.

Patients will be instructed on the method of administration and provided with an instruction sheet.

The drug can be administered at any time during the day, but the same time should be used each day. Twice daily doses should be administered at approximately 8 to 12hour intervals and for three times daily dosing, first dose to be administered in the morning and two doses administered should be administered at approximately 8-12 hours later. A missed dose should be taken as soon as it is noted as missed. Taking two suppositories at the same time is permitted in order to catch up a missed dose within a day. No more than three suppositories should be taken in a 24-hour period.

9.3 RADIATION THERAPY

External beam radiation therapy will be applied to a minimum of one or more selected lesions in 5 daily fractions, over five to eight days, at a dose of 20Gy.

The number of lesions to be irradiated will be at the discretion of the investigator as clinically indicated. Lesions which directly receive radiotherapy will be categorized as “irradiated lesions” with all other lesions identified as “non-irradiated lesions”.

Lesions will be assessed by the investigational site at screening and any symptomatic lesion/s for irradiation which can be assessed by RECIST 1.1 criteria will be noted as “measurable irradiated target lesions” and symptomatic lesions that cannot be measured will be noted as “non-measurable lesions”. Further detail is provided in Section 10.4.8. Lesions will be captured by CT or MRI scan at baseline with follow-up CT/MRI imaging at Week 6, Week 12 and Week 24. Scan image data will be stored on central planning system software (such as *MIM*) for radiological comparisons and response to treatment will be reported.

During screening period, baseline lesion/s will be selected for irradiation and the gross tumour volume (GTV), the clinical target volume (CTV) and organs at risk (OAR) will be defined by the radiation oncologist based ICRU 50 or ICRU 83 guidelines.

Radiation therapy will be delivered to target labelled irradiation lesions according to the study radiation treatment plan developed. Details are provided in the NOX66-002A **Radiation Therapy Planning, Delivery and QA Guidelines** which must be used as the primary source for planning and delivering radiation therapy treatment within the trial.

Tumour lesions either for irradiation or not which, at baseline, are identified as measurable will be noted as target lesions and will be assessed for response to treatment according to RECIST 1.1 criteria. Symptomatic tumour lesion which at baseline is identified for irradiation but not measurable will be noted a non-measurable target lesion/s.

All radiological scans during the study will be reviewed by the independent Radiation Oncology Expert Committee for each patient to assess overall response to treatment.

9.4 TREATMENT DOSE MODIFICATIONS AND TREATMENT CYCLE DELAY

9.4.1 NOX66

Any patient who experiences toxicity > Grade 2 related to NOX66 will have the idronoxil treatment withheld for 1 day and then resume on the next lower dosage (1200 mg reduced to 800 mg; 800 mg reduced to 400 mg; 400 mg daily reduced to 400 mg every 2nd day) for the remainder of the treatment period.

If toxicity > Grade 2 persists following reduction of dose, the idronoxil treatment will cease immediately for the remainder of the treatment period, although the patient may remain in the study.

There will be no dose modification of NOX66 on the basis of body weight.

9.4.2 Radiation Therapy

There will be no dose modification of radiation therapy. Any deviation from the planned dose of radiation therapy will be reported by the investigator in the CRF.

9.5 ACCOUNTABILITY FOR CLINICAL SUPPLIES

The Principal Investigator or delegate/s will be responsible for the dispensing, inventory, and accountability of all clinical supplies, exercising accepted medical and pharmaceutical practices. An accurate and timely accountability record log of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection by the Sponsor or the designated Sponsor's representative upon request. All used medication packaging and unused medication will be collected and retained until completion or termination of the study. Once all drug accountability has been performed and monitored the Investigator or delegate/s will destroy NOX66 as per Site Pharmacy SOPs and/or return all remaining clinical supplies to the Sponsor who will destroy the study drug on the site's behalf. Under no circumstances will the Principal Investigator allow NOX66 to be used other than as directed by this protocol.

9.6 CONCOMITANT MEDICATIONS

Patients are permitted a wide range of medications for general health, although this is to be confirmed with the Sponsor prior to enrolment into the Study.

Patients are permitted certain medications specifically related to their metastatic disease, including use of androgen deprivation therapy (ADT) such as luteinizing hormone-releasing hormone (LHRH) agonists and antagonists. Other therapies are to be confirmed with the Sponsor medical monitor prior to enrolment in the Study.

Patients are not permitted any other experimental treatments. Supportive care measures and treatment for symptom control are permitted, including analgesics. Treatment of constipation or diarrhea is permitted however the investigator must determine the suitability of these patients to continue taking suppositories should these adverse events (as scored by NCI CTCAEv4.03) be reported. Patients will be medically monitored so that any adverse events will be identified promptly and treated appropriately.

Details regarding the name, indication, route of administration, dose, and frequency of all medications taken within 14 days prior to study drug administration will be recorded in the eCRF at the Screening Visit and Day 1. Details regarding the name, indication, route of administration, dose, and frequency of all medications taken during the study will be recorded in the eCRF at each patient visit. “All medications” should include prescription, over-the-counter (OTC) medications, dietary/nutritional supplements, and herbal products.

10 STUDY PROCEDURES

10.1 OUTCOME MEASURES

The outcome measures supporting the primary objective of this study are:

- Number of events of > Grade 2 toxicity (as scored by CTCv4.03)
- Number of events of > Grade 2 toxicity considered by the investigator and / or the Sponsor as causally related to the use of NOX66 (as scored by CTCv4.03)
- The overall number of adverse events considered by the investigator and / or the Sponsor as causally related to the use of NOX66
- Incidence of dose limiting toxicities (DLT) and or maximum tolerated dose (MTD) of NOX66

The outcome measures supporting the secondary objectives of this study are:

- Where target (measurable) lesions have been identified:
    a. Change intumour size of irradiated lesions according to RECIST1.1 criteria, as assessed by central review and by the investigator based on CT/MRI scan
    b. Change in tumour size of target non-irradiated lesions according to RECIST1.1 criteria, as assessed by central review and by the investigator based on CT/MRI scan
    c. Observation of change from baseline in Non-target lesions according to RECIST 1.1 criteria
- For all patients – overall assessment of change in disease state by an independent Radiation Oncology Expert Committee
- Change from baseline in pain score based on responses to BPI-SF
- Observation of change from baseline in PSA levels
- Assessment of patient via physical exam and ECOG Score

- Plasma level of idronoxil post treatment (immediate and long term (at 6 weeks))
- Duration of tumour progression free state from study treatment start date
- Duration of survival from study treatment start date

10.2 STUDY VISITS

The total study duration per patient will be a minimum of 25 weeks, with continued follow up up to 24 months from the treatment commencement date:

- Screening period: to occur within 2 weeks prior to the scheduled date of treatment commencing
- Treatment and follow up period: up to 24 weeks from the commencement of the first dose of NOX66 and it includes enrolment visit to occur prior to Day 1 of treatment
  Long term follow up visits: every 3 months from week 24 for another 18 months. Observation period (post study follow-up visits): Continued observation of patients beyond 24 months follow up visit, at the discretion of the investigator.

10.2.1 Screening Visit (VS)

The purpose and the procedures of the Study will be fully explained to participants at the screening visit and every patient approached regarding the study will be provided with the Informed Consent Form (ICF). Patients wishing to enrol in the Study will sign the ICF prior to initiating any study related investigations or procedures.

All screened patients who sign the ICF must be recorded on the Screening/Enrolment Log. If a patient who signs an ICF is not enrolled in the study, the reason will be noted. The Screening/Enrolment Log will be retained within the Investigator Site File.

The following procedures are to be performed at the screening visit to occur within 2 weeks of commencement of NOX66 treatment:

- Obtain Informed Consent
- Review and confirm eligibility (Inclusion / Exclusion Criteria)
- Medical History and Demography, including review of any prior radiation therapy and toxicities / adverse events
- Physical Examination including vital signs
- Performance Status Assessment (using ECOG performance scale)
- Safety blood sampling – Complete Blood Count, Serum Chemistry, and Urinalysis; and results within 5 days of enrolment
- Blood sample for serum PSA and testosterone
- Electrocardiography (12-lead) in triplicate
- Concomitant Medication Review
- Tumour Imaging (CT/MRI) including measures of target lesions- baseline
- Administration of Brief Pain Inventory -Short Form questionnaire

Radiological scans performed prior to consent may be utilized for the purposes of the study if they have been performed as part of routine clinical practice and the patient consents for their medical records to be reviewed by the Sponsor, the scans were performed in the 28 days prior to the screening visit (i.e. they can be considered current evidence of tumour size) and they can provide suitable tumour measurements and assessments of target and non-target lesions.

The Principal Investigator will maintain a confidential log of all patients who have been screened for participation in the study whether or not the patient was eligible for study participation

10.2.2 Enrolment Visit (V1):

Once eligibility is confirmed patients will be contacted to attend clinic for:

- education on self-administration and dispensing of NOX66 for use from Day 1 of the treatment cycle
- baseline biomarker blood sample for idronoxil

Patient may be contacted by telephone after enrolment as a reminder to start NOX66 administration day prior to attending clinic for radiation therapy.

10.2.3 Treatment Cycle (Days 1-16) - Visits 2 to 7

Treatment will Commence on Day 1 of the Study Visit Schedule (Table 1) and the procedures for Treatment Visits are listed below in Table 1.

Overall, the patient will attend the clinic on 7 days during the Treatment Cycle.

During the Treatment Cycle, the patient will receive treatment of:

- NOX66 (Dose dependent on treatment cohort) for 13 up to 16 consecutive days (Days 1-16), inclusive of weekends and public holidays.
- Palliative radiation therapy (20Gy Dose) in five fractions over 8 days commencing on Day 2 to Day 9. Radiation therapy **not given** on weekends and public holidays.

Table 1. Schedule of Assessments: TREATMENT CYCLE

Period	Pre-RT		RT								Post RT						EoT[3]
	D0 (-7)	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 9	D 10	D11	D 12	D 13	D 14	D 15	D 16±1
VISITS	V1[1]		V2	V3 - V6[2]													V7
NOX66 (Self-administration)		X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]		
Radiation therapy			X	X													
Physical exam			X														X
ECG																	X
Vital Signs			X														X
Complete Blood Count																	X
Serum chemistry																	X
Urinalysis																	X
Biomarker[5]	X																X
BPI-SF[6] Questionnaire																	X
Concomitant medications/ Adverse Event[7] review			X	X													X
Dispense NOX66	X																
Return NOX66																	X

[1]Enrolment-Visit to occur after eligibility confirmation (Screening) and prior to V2, to receive NOX66 and education on self-administration

[2] Patient attend clinic for 5 days in an 8-day period to receive RT. Patient will not attend clinic on days where RT is not conducted

[3] End of Treatment (EoT) visit to occur Day following last dose of NOX66

[4]NOX66 dosing continues to Day 16 if there has been (weekend and public holiday -up to 3 days) interruption in RT in Treatment Cycle.

[5] Biomarkers include idronoxil

[6] Brief Pain Inventory-Short Form (1991)

[7] Adverse Event (AE) assessed by Investigator using the NCI CTCAE v4.03 scoring system

10.2.4 Six-Week Follow up (Day 43 ± 5) - Visit 8

Visit 8 will occur 28 days/4 weeks post completion of NOX66 treatment and consist of the following assessments:

- Physical Examination including vital signs
- Performance Status Assessment (using ECOG performance scale)
- Safety blood sampling – Complete Blood Count, Serum Chemistry and Urinalysis
- Biomarker blood sampling – PSA and idronoxil
- Administration of Brief Pain Inventory -Short Form questionnaire
- Concomitant Medication Review
- Adverse Event Review (CTCAE 4.03)
- Tumour Imaging (CT/MRI scan) and Assessment

10.2.5 Twelve-Week Follow up (Day 84 ± 7) - Visit 9

Visit 9 will occur 70 days/10 weeks post completion of NOX66 treatment and consist of the following assessments:

- Physical Examination including vital signs
- Performance Status Assessment (using ECOG performance scale)
- Electrocardiography in triplicate
- Safety blood sampling - Complete Blood Count, Serum Chemistry and Urinalysis
- Biomarker blood sampling – PSA
- Administration of Brief Pain Inventory -Short Form questionnaire[1]
- Concomitant Medication Review
- Adverse Event Review (CTCAE 4.03)
- Tumour Imaging (CT/MRI scan) and Assessment

[1] If pain score from assessment of response to BPI-SF questionnaire demonstrates an improvement in pain (refer to section 10.4.5) a confirmatory questionnaire at least 2 weeks later will be verbally administered to patients as described for 18-week administration of BPI-SF.

10.2.6 Eighteen -Week administration BPI-SF (Day 125 ± 5)

The Brief Pain Inventory- Short Form questionnaire will be verbally administered to patients by site staff via the telephone. Site staff will schedule a suitable time with the patient to conduct the phone interview and document patient responses.

10.2.7 Twenty-Four Weeks Follow up/ end of study (Day 168 ±7) -VISIT 10

Visit 10 will occur 154 days/22 weeks post completion of NOX66 treatment and consist of the following assessments:

- Physical Examination including vital signs
- Performance Status Assessment (using ECOG performance scale)
- Electrocardiography in triplicate
- Safety blood sampling - Complete Blood Count, Serum Chemistry and Urinalysis
- Biomarker blood sampling – PSA
- Administration of Brief Pain Inventory -Short Form questionnaire
- Concomitant Medication Review
- Adverse Event Review (CTCAE 4.03)
- Tumour Imaging (CT/MRI scan) and Assessment

All patients currently in the study or follow up period, will be asked to re-consent with the revised ICF in order to agree to participate for additional follow up visits (Visit 11 to 16).

For patients who have withdrawn from the study prior to study completion or completed End of Study visit (Visit 10) at the time of this amendment implementation, the investigator or designee will make contact by phone to seek patient willingness to participate in long term follow up and if the patient agrees, a visit will be scheduled for reconsenting.

For Patients who have completed End of Study Visit (Visit 10) at 24 weeks and are unable to be contacted or are > 6 months post EOS, the Investigator or designee at each study site will review medical records from End of Study visit to most recent information available and report on:

- Disease status based on available radiology or other assessments
- Patient Survival information
- Any new anti-cancer treatment after discontinuation of study treatment

10.2.8 Month 9 Long Term Follow up -Visit 11

Visit 11 will occur approximately 3 months after 24 weeks follow up (Visit 10) and consist of the following assessments:

- Performance Status Assessment (using ECOG performance scale)
- Biomarker blood sampling – PSA
- Administration of Brief Pain Inventory -Short Form questionnaire
- Tumour Imaging (CT/MRI/US scan) and Assessment
- Report of any pain medication and any anti-cancer treatment after discontinuation of study treatment

10.2.9 Month 12 Long Term Follow up -Visit 12

Visit 12 will occur approximately 6 months after 24 weeks follow up (Visit 10) and

consist of the following assessments:

- Performance Status Assessment (using ECOG performance scale)

- Biomarker blood sampling – PSA
- Administration of Brief Pain Inventory -Short Form questionnaire
- Tumour Imaging (CT/MRI/US scan) and Assessment
- Report of any pain medication and any anti-cancer treatment after discontinuation of study treatment

10.2.10 Month 15 Long Term Follow up -Visit 13

Visit 13 will occur approximately 3 months after the previous visit and consist of the following assessments:

- Biomarker blood sampling – PSA
- Tumour Imaging (CT/MRI/US scan) and Assessment
- Report of any pain medication and any anti-cancer treatment after discontinuation of study treatment

10.2.11 Month 18 Long Term Follow up -Visit 14

Visit 14 will occur approximately 3 months after the previous visit and

consist of the following assessments:

- Biomarker blood sampling – PSA
- Tumour Imaging (CT/MRI/US scan) and Assessment
- Report of any pain medication and any anti-cancer treatment after discontinuation of study treatment

10.2.12 Month 21 Long Term Follow up – Visit 15

Visit 15 will occur approximately 3 months after the previous visit and

consist of the following assessments:

- Biomarker blood sampling – PSA
- Tumour Imaging (CT/MRI/US scan) and Assessment
- Report of any pain medication and any anti-cancer treatment after discontinuation of study treatment

10.2.13 Month 24 Long Term Follow up -Visit 16

Visit 16 will occur approximately 3 months after the previous visit and

consist of the following assessments:

- Biomarker blood sampling – PSA
- Tumour Imaging (CT/MRI/US scan) and Assessment

- Report of any pain medication and any anti-cancer treatment after discontinuation of study treatment

Patients who have disease progression during any of the follow up periods between Visit 10 and Visit 16, will be followed up for survival information by the Investigator or designee via a telephone contact.

All data collected from Visit 11 to 16 will be entered in a paper CRF provided by the Sponsor or delegate.

10.2.14 Cohort Allocation and Dose Escalation

This study will enrol up to 24 patients across three dose levels of NOX66. Dose cohort assignment will be sequential and dose escalation decisions will be based on patients who experience adverse events directly related to NOX66 treatment and discontinued as described below and outlined in Figure 2.

Dose escalation and decision rules are as follows:

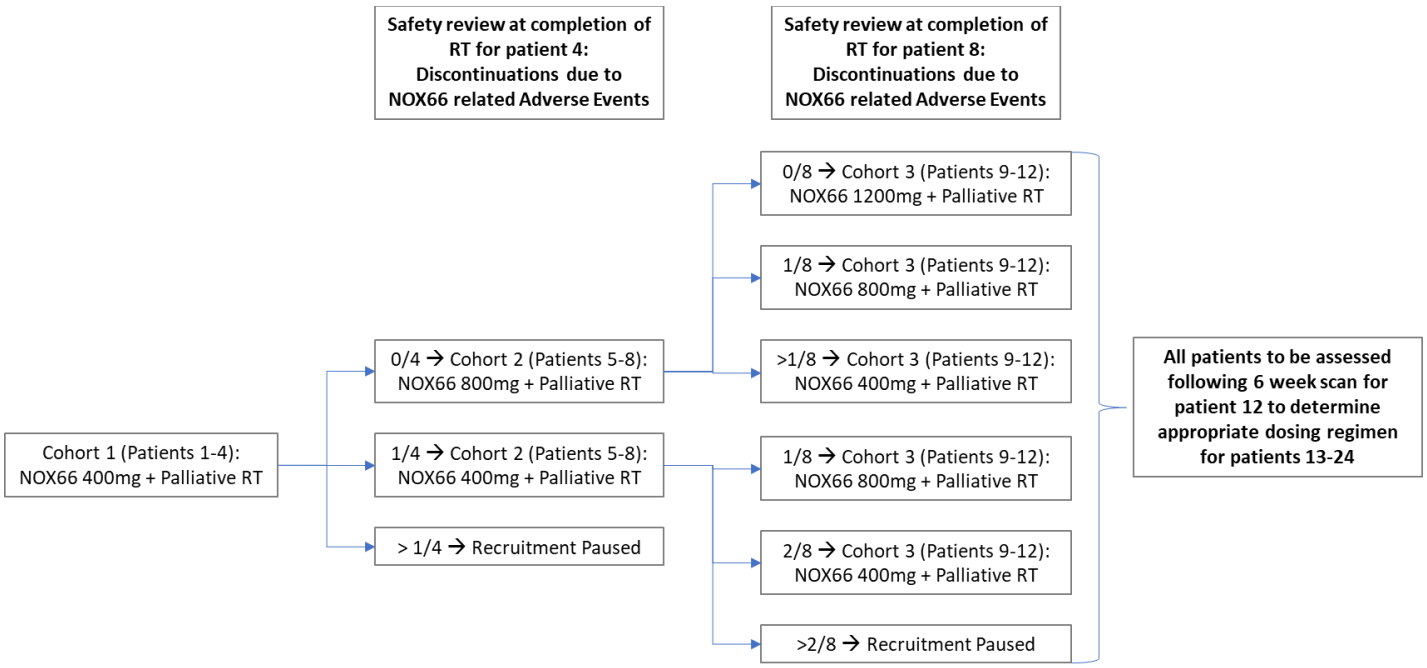
- **Patients 1-4 (Dose Cohort 1)** will be prescribed NOX66 400mg.

- **Patients 5-8 (Dose Cohort 2):** Once fourth patient in Cohort 1 has completed treatment (Visit 7), the dose of NOX66 for next cohort, patients 5-8, will be as determined as follows, based on the number of discontinuations due to NOX66 related adverse events:
    - If no patients discontinue treatment, NOX66 dose will be increased to 800mg
    - If one patient discontinues treatment, NOX66 dose will remain at 400mg
    - If more than one patient discontinues treatment, there will be no further recruitment to the study until scans from WEEK 6 are assessed for disease status

- **Patients 9-12 (Dose Cohort 3)**: Once the eighth patient in Cohort 2 has completed treatment (Visit 7), the dose of NOX66 for next cohort, patients 9-12, will be as determined as follows, based on the number of discontinuations due to NOX66 related adverse events:
    - If no patients in Dose Cohort 2 discontinue treatment, NOX66 dose will be increased (from 400mg to 800mg or from 800mg to 1200mg)
    - If one patient in Dose Cohort 2 discontinues treatment, NOX66 dose will remain at the same dose (400mg or 800mg)
    - If more than one patient in Dose Cohort 2 discontinues treatment, dose will be reduced (from 800mg to 400mg) or, if dose has remained at 400mg, there will be no further recruitment to the study until scans at WEEK 6 are assessed for disease status.

Following the review of all accumulated safety data, disease status and treatment efficacy signals from scans assessed per RECIST 1.1 criteria and preliminary pain response at WEEK 6 for all patients, the Study Steering Committee will determine the dose at which to continue treatment for the expansion patient Cohort 4 in the study. A further 12 patients will be recruited at this dose level.

Figure 2: Dose Escalation and Dose Expansion Schema



10.3 POST STUDY OBSERVATION

After 24-month long term follow up, the investigator may report any changes in outcomes for patient specifically related to:

- Progression of disease or relapse
- Survival information

10.4 CLINICAL ASSESSMENTS

10.4.1 Medical History and demography

Medical history will include demographic data (e.g., date of birth, race/ethnicity) and additional relevant medical information including:

- all medical conditions and disease states that require current or ongoing therapy, and
- other medical conditions and disease states that, in the opinion of the Investigator, are relevant to the patient's study participation

10.4.2 Physical examination

The physical Examination performed in this study will include height, weight, blood pressure, pulse and body temperature and a physical (external) assessment of the patient. Blood pressure and pulse may be measured whilst the patient is sitting or lying but must be measured consistently for the patient throughout the study. Temperature should be measured in accordance with the centre's standard practice. Any significant abnormalities noted during the physical examination at screening should be reported in the Medical History. Any significant changes noted on follow up physical examination should be reported as adverse events.

10.4.3 ECOG Performance assessment

A patient's performance Status will be assessed using the Eastern Co-operative Oncology Group (ECOG) Performance Score (Appendix 1).

10.4.4 Electrocardiography

12-lead ECGs will be taken using a serviced and calibrated machine in triplicate, within 5 minutes of each other (over 15 minutes), to calculate the mean QTc value to ensure the patients eligibility for study enrollment. ECGs should be taken after the patient has been resting supine for 5 minutes.

ECG will be performed at three timepoints throughout the study – Screening, End of Treatment visit and end of study. Any abnormalities noted during the physical examination at screening should be reported in the Medical History. Any changes noted on follow up ECG on should be reported as adverse events.

10.4.5 Brief Pain Inventory-Short Form

Pain will be evaluated using the Brief Pain Inventory-Short Form instrument (Appendix 2). Total score is an average of the pain interference score (mean value for the nine BPI-SF items) and pain subscale score (mean value for the nine BPI-SF items 3,4,5 and 6).

Questions on pain interference inquiring about extent of interference with activities by pain on scale of 0 (does not interfere) to 10 (completely interferes).

Questions on pain inquire about extent of pain on scale of 0 (no pain) to 10 (pain as bad as you can imagine).

Total score ranges from 0 to 10 with higher values indicating more pain.

The BPI-SF questionnaire will be administered at six timepoints throughout the study-Screening (baseline), End of Treatment visit 7, at Week 6, 12, 18 and 24 post treatment.

Overall pain improvement response is defined as a decrease in pain score greater or equal to 30% at 12 weeks relative from baseline without overall increase in opiate use and confirmed at least 2 weeks later per PCWG3 guideline[41].

10.4.6 Safety Blood Sampling

Non-fasting samples for clinical laboratory analysis will be collected as listed below:

- Complete blood count (CBC) including: white blood cells with differentials, red blood cells, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelet
- Serum chemistry panel including sodium, potassium, calcium, creatinine, total protein, albumin, bilirubin (total, direct), AST/SGOT, ALT/SGPT, alkaline phosphatase (ALP)
- Urinalysis dipstick - Clarity, specific gravity, pH, protein, glucose, ketones, nitrite, leukocytes, and blood. Urine microscopy will be performed if urinalysis values are out of range and the Investigator deems that the microscopy is clinically warranted

Haematology, clinical chemistry and urinalysis will be performed by the site's local accredited laboratories.

10.4.7 Biomarker Sampling

- PSA levels will be collected at baseline, and post treatment cycle at Visit 8 (Day 43), Visit 9 (Day 84) , Visit 10 (Day 168) and Visit 11 – Visit 16 (every 3 months after Visit 10) to determine any response to treatment. PSA samples will be collected by standard practice and analysed at each site's local laboratory.
  Idronoxil: Plasma samples will be collected at baseline and Visit 7 (Day 16±1) of treatment cycle and post treatment at Visit 8 (Day 43) to determine levels of any accumulation during and post treatment. Instructions for idronoxil plasma collection will be provided by Sponsor and analysis will be undertaken by the Sponsor performed by a designated laboratory.

10.4.8 Tumour Imaging

Tumour imaging by CT/MRI will be performed in line with local practices using a planning software system.

Baseline documentation of Target and Non-Target lesions

'Target' lesions are assessed at the designated scanning time points and defined as lesions that are measurable and:

Irradiated, such as soft tissue and lytic bony lesions, have defined margins for measurement and are irradiated at the discretion of the investigator. These lesions will be noted as 'irradiated measurable target'.

- Non-irradiated and these lesions will be noted as 'non-irradiated measurable target'.

For measurable lesions, the Longest Diameter (LD) of each lesion will be measured and a sum of the LD will be calculated and reported as the baseline sum LD. The sum LD will be used as reference by which to characterize the objective tumour response based on RECIST v1.1 criteria (see below).

Patients will undergo baseline CT or MRI body scan. A maximum of 5 lesions in total, with no more than 2 lesions per organ, will be identified as target lesions.

'Non-Target' lesions include all other lesions and are recorded at baseline as either measurable or non-measurable. For non-measurable lesions, the presence or absence of each will be noted throughout follow-up scanning time points. For measurable lesions, size (mm) will be noted throughout follow-up scanning time points.

These can include irradiated lesions such as sclerotic bone lesions, which do not have defined margins for measurements and are irradiated at the discretion of the investigator. These lesions will be assessed for local response based on patient reported outcome using the BPI-SF (see section 10.4.5).

Review of all CT/MRI scans per patient will be conducted by the independent Radiation Oncology Expert Committee as outlined in Section 10.4.9.

RECIST evaluation of target lesions

Assessment of irradiated measurable lesions will be conducted according to the RECIST1.1 Criteria for response on the CT or MRI scan, as set out below.

Complete Response (CR):	Disappearance of all relevant target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of relevant target lesions, taking as reference the baseline sum LD
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of relevant target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Evaluation of non-target lesions

Non-measurable Assessment:

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level

Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Measurable Assessment:

Response	Percent change in lesion size based on sum LD (mm) taking as reference the baseline sum LD.

10.4.8.1 Radiological assessment of tumours during long term follow up period (Visit 11-16)

Radiological assessments will be at the discretion of the investigator. The disease status assessment will be based on local radiology results. No central radiographic assessment will be undertaken during the long term follow up period.

10.4.9 Radiation Oncology Expert Committee

A Radiation Oncology Expert Committee (ROEC), comprising medical Oncologists, Radiation Oncologists and Radiologists independent of the study sponsor, will be formed to assess clinical progression of patients on the study. The ROEC will receive copies of all CT/MRI scans (including any with RECIST measures), PSA measures, ECOG and pain score measurements for review and provide an assessment of overall clinical evaluation of response per patient which will be documented according to sponsor guidelines. This assessment will be used to support the definition of endpoints for future studies.

11 DATA COLLECTION AND MANAGEMENT

11.1 METHODS

It is the responsibility of the Principal Investigator to ensure that there will be primary source documentation for all patient data collected as part of the study, and the data will not be recorded onto the eCRFs without the availability of such primary documentation. For this study, there is no data which has been permitted for direct data entry without source documentation. The source data may include such documents as clinical notes, laboratory result sheets, pathology reports, radiology results, etc., and will be retained in each patient's medical record or research chart. CRFs will be provided by the Sponsor.

The Principal Investigator or delegate/s will be responsible for the timeliness, completeness, and accuracy of the information entered on the CRF. The Principal Investigator will provide

access to the Medical Monitor or designated Sponsor representative(s) for the periodic review of all study records, source documents among other records for review and inspection to assure accuracy and completeness of the CRFs. All CRFs will be 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each patient.

The Sponsor and designated Sponsor representative(s) will maintain frequent contact with each site to assure the study is conducted according to the protocol and that all data collected are accurate and complete. Any deficiencies identified during the study will be communicated to the site for prompt correction.

11.1.1 Case report form

All information relative to the study will be recorded into a 21 CFR part 11 FDA compliant electronic Case Report Form (CRF). Data corrections will be entered by the authorised site personnel.

11.1.2 Return and storage of forms

The Investigator will retain the copies of the CRF and all other study related documents for 15 years from completion of the study.

11.2 DATA MANAGEMENT

11.2.1 Data Coding

Medications will be coded from the WHO Drug Dictionary and medical history and adverse events will be coded using the MedDRA terminology for System Organ Class (SOC) and Preferred Term (PT).

11.2.2 Data validation

A Data Management Plan which fulfils the requirements for ICH GCP will be developed to describe all manual and electronic validation checks of the data prior to analysis. Data queries requiring clarification will be documented on the EDC eCRF for the investigational site to resolve. Only authorised personnel will make corrections to the clinical database, and all corrections will be documented in an electronic audit trail.

12 STATISTICAL SECTION

12.1 SAMPLE SIZE

The study is intended as a Proof of Concept and dose confirmation study, providing justification for and guidance on the design of further studies.

The primary objective of this study is to observe safety and tolerability of idronoxil (NOX66) in combination with radiation therapy (at palliative doses). In conjunction with observations

from the other phase 1 trials in the NOX66 development program, 24 patients are considered adequate to inform on toxicity and safety in order to progress to phase 2/3.

Palliative Radiation therapy alone is unlikely to provide more than a minor and temporary reduction (<30%) in tumour size. Any responses greater than this will be considered to be related to NOX66 use. Any signals of efficacy will be described in the Clinical Study Report and used to support the Phase 2/3 development program.

12.2 STATISTICAL METHODOLOGY

This section describes the planned statistical analyses in general terms. A complete description of the statistical analysis will be specified in a statistical Analysis Plan (SAP) finalised prior to completion of the study.

General: Data will be summarized by using counts and percents for discrete parameters, and by descriptive statistics (e.g. number of observations, mean, standard deviation, median, minimum and maximum) for continuous parameters. Subject disposition and baseline characteristics will be presented for all treated patients. Data will be analysed as collected. No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of the data.

Populations for analysis: There will be two study populations defined for this study. The safety population will consist of all patients who received at least one dose of NOX66. This population will be used in all safety summaries. The efficacy population will consist of all patients who complete radiation therapy with at least 7 days of NOX66 dosing.

Baseline Comparisons and Patient Disposition: Demographic and baseline disease characteristic data summarisation will be performed in order to descriptively document any safety and efficacy findings. Data to be tabulated will include demographic features such as age and race, as well as medical history. The number and percentage of patients who complete the study or who withdraw for any reason will be presented.

Efficacy Analysis: Results from (i) RECIST 1.1 response assessment for target lesions and non-target lesions, (ii) ECOG Performance Score and (iii) Pain scores. Changes form baseline in levels of serum PSA levels will be listed.

Overall and progression-free survival, PSA and pain scores collected during the extended follow-up period will be summarized in the same manner as for the immediate post-treatment follow-up period.

Safety Analysis: The safety will be assessed through the analysis of the reported incidence of treatment emergent AEs, including SAEs, dose-limiting toxicities, AEs leading to withdrawal, events of at least CTCAE Version 4.03 Grade 3 in severity, and AEs related to study treatment. Treatment emergent AEs are those with an onset on or after the initiation of therapy. Other safety endpoints include laboratory results, physical examinations, vital signs, and changes in ECOG status. A copy of CTCAE Version 4.03 scoring system may be downloaded from:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The adverse events will be summarized by MedDRA coding terms, System Organ Class (SOC), and preferred term for all treated patients and by dose cohort. The AEs will also be tabulated by maximum severity and maximum relationship to study drug where applicable. The number and percent of patients experiencing dose-limiting toxicities will be summarized by dose cohort, by DLT, and system organ class for all treated patients. Other safety endpoints, which include change from baseline in laboratory results and vital signs, and shifts in physical examinations, will be summarized throughout the study by visit for each dose level for all treated patients.

Concomitant medications: are to be listed for all patients.

12.3 PROCEDURES FOR HANDLING MISSING, UNUSED AND SPURIOUS DATA

No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of the data

Interim analysis

Interim analyses will be conducted after last patient in dose Cohort 3 has completed 6-week follow up (Visit 8) and will be used to determine the progress of the study and dose decision for expansion Cohort 4. Further analysis will be conducted after each cohort has completed 12 and 24 weeks follow up (Visit 8 and 10).

13 MONITORING

13.1 MONITORING OF CASE REPORT FORMS

The study will be monitored by a CRO on behalf of the Sponsor. Monitoring will be conducted per ICH GCP guidelines and Sponsor SOPs. The Monitor will visit the Investigator at regular intervals to review the progress and conduct of the study. The CRFs will be checked for completeness and accuracy against the patient records, charts, laboratory reports, and scans. Anonymity of the patient will be maintained at all times.

13.2 SAFETY DATA MONITORING

The Study Steering Committee (SSC) will review and evaluate all toxicities causally associated with NOX66 treatment and or the radiation therapy combination therapy. The SSC will consist of:

- Principal Investigator from each clinical site, or medical designee
- Sponsor's Medical Monitor
- CRO Medical Representative (if applicable)
- Director of Clinical Development, Noxopharm Ltd

Review of any adverse events of Grade 2 toxicity and above, considered by the Principal Investigator to be related to idronoxil (NOX66), will be reported to the SSC immediately and decision on the continuation of the patient individually, and the study in general, will be provided.

The Study Steering Committee will review the Safety Data and determine dose cohort escalation following completion of treatment cycle (Visit 7) of final patient in a cohort.

The SSC will determine the dose for cohort expansion based on the review of accumulated safety data, on treatment response and disease evaluation following WEEK 6 assessments of all patients and determine continuation of the study.

13.3 AUDITING

Regulatory authorities, the HREC/EC or the Sponsor may request access to patient clinical notes and other relevant study documentation for an on-site audit or inspection at any time during or after study completion. The Investigator is obliged to facilitate this process by allowing full access.

14 ADVERSE EVENTS REPORTING

Adverse events (AE) or serious adverse events (SAE) reported by the patient or observed by the Investigator will be listed individually on an adverse event form in the CRF. The signs and symptoms, time of onset, duration, treatment (if any), and follow-up procedures (if any) will be reported, and the criteria for assessing causality to study drug and outcome categories should be defined.

Pre-existing conditions or illnesses which are expected to exacerbate or worsen are not considered adverse events and will be accounted for in the patient's medical history.

All adverse events are to be followed up for 30 days following the end of study or until resolution (whichever is sooner).

In order to classify AEs and diseases, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF using the Medical Dictionary for Regulatory Activities (MedDRA).

14.1 DEFINITIONS

14.1.1 AE

AE is any un-anticipated or unintended medical occurrence or worsening of a sign or symptom (including an abnormal laboratory finding) or disease in a study participant, which does not necessarily have a causal relationship with the study condition, procedures or study agent(s) that occurs after the informed consent is obtained.

14.1.2 SAE

An SAE is defined as any untoward medical occurrence that results in death, is immediately life-threatening, requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited 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 intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Progression of malignancy (including fatal outcomes), if documented by the use of an appropriate method (for example, as per RECIST 1.1 criteria for solid tumours), should not be reported as an SAE and must be approved by the Sponsor.

Treatment within or admission to the following facilities does not meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial), does not require reporting as a SAE to the Medical Monitor and Sponsor.

The definition of "related" is that there is a reasonable possibility that the drug caused any of the adverse events described in Table 2.

14.1.3 Guidelines for determining causality and severity

The criteria used for determining the relationship between the study drug/s and the Adverse Event are shown in Tables 2 and 3:

Table 2 Criteria for determining relationship between AE and idronoxil (NOX66)

Unlikely/unrelated:	An AE with a temporal relationship to drug administration, which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	An AE with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Likely	An AE with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (rechallenge). Rechallenge information is not required to fulfil this definition
Certain	An AE occurring in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drugs should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using a satisfactory rechallenge procedure if necessary and feasible

Table 3. Adverse event outcome categories

Resolved'	The patient has fully recovered from the adverse event with no residual effects observable.
'Resolved with Sequelae'	The patient has recovered from the adverse event, however there are residual effects observable.
'Ongoing'	The adverse event is still present and observable.
'Death"	The patient died as a result of the adverse event.
'Unknown'	The outcome of the adverse is unknown at the time of report.

14.2 RESPONSIBILITIES FOR REPORTING

Investigators and the Sponsor are required by regulatory agencies worldwide to report adverse events which involve patients being administered a pharmaceutical product.

All serious adverse events (SAE) occurring from the signing of informed consent until 30 calendar days after last study visit whether related to drug or not, must be reported to the Medical Monitor and appropriate Sponsor contact person within 24 hours of first knowledge of the experience using the appropriate study SAE Report Form. SAEs are to be followed until resolution or stabilisation (with autopsy report if applicable).

Although pregnancy is not a formal SAE, if the study participant or the partner of a study participant becomes pregnant while the study participant is on study, the pregnancy is to be reported on the pregnancy report form via the SAE process.

Deaths and other SAEs occurring > 30 calendar days after last study visit that are deemed 'possibly' or 'probably' related to the study treatment must be reported as SAEs on the SAE Report Form within 1 day of first knowledge of the event by the treating physician or research personnel (with an autopsy report if available).

Deaths occurring > 30 calendar days after last study visit and not attributed to study treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate CRF.

The investigative sites will send the SAE report to the Sponsor's Medical Monitor via fax or e-mail and to the Sponsor's pharmacovigilance manager using the contact information below.

Primary Contact Professor Paul de Souza	Tel: +61 404 003 220 Email: P.DeSouza@westernsydney.edu.au
Alternate Contact Study Manager: Marinella Messina	Tel: + 61 2 9144 223; Fax: + 61 2 9199 9600 Email: marinella.messina@noxopharm.com
Pharmacovigilance (DATAPHARM Australia) Manager: Hong-Van Dang-Beck	Tel #: 61 2 9719 2800; Fax #: 61 2 9719 2811 Email: hongvan.dangbeck@datapharmaustralia.com

Transmission of the SAE Report Form should be confirmed by the site personnel submitting the report. The first report must contain as minimum the study ID, patient number, a description of the event, the name of the investigational product, estimate of causality and the name of the person reporting the event.

14.2.1 SAE and Unresolved AE Follow-Up

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Medical Monitor as soon as possible using the SAE Report Form.

The patient should be followed until it is determined that the event resolved, stabilized, or in the opinion of the Investigator the event is not going to improve due to underlying disease, or the patient is lost to follow-up.

Investigators must report SAEs and follow-up information to their responsible HREC according to the policies of the responsible HREC.

The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

14.2.2 Investigator Reporting of AEs/SAEs/Deaths after Study Discontinuation

Thirty days after completing protocol-specific treatment or study discontinuation, treatment related AEs, SAEs, or deaths determined by the Investigator as treatment related are to be reported directly to the Sponsor.

At the last scheduled study visit, the Investigator should instruct the patient to report to the Investigator any subsequent SAEs that the patient or the patient's personal physician believes could be related to prior study treatment.

SAEs after study discontinuation considered related to study treatment are to be sent to the Sponsor.

14.2.3 Sponsor SAE Reporting Requirements

The Sponsor is responsible for reporting relevant SAEs/Suspected Unexpected Serious Adverse Reactions **(SUSARs)** to the competent authority, regulatory authorities (e.g. TGA), and participating investigators, in accordance with International Council on Harmonization (ICH) guidelines and/or local regulatory requirements.

The Sponsor is responsible for reporting **unexpected fatal or life-threatening events** associated with the use of the trial drugs to the regulatory agencies and competent authorities via telephone or fax **within 7 calendar days** after being first notified of the event. The Sponsor will report all related but unexpected SAEs including **non-death/non-life-threatening related but unexpected SAEs** associated with the use of the trial medications to the appropriate competent authorities (according to local guidelines), investigators, and relevant HREC by a written safety report **within 15 calendar days of notification**.

15 CONDUCT OF STUDY

15.1 HUMAN RESEARCH

The Protocol and all other relevant study documents (informed consent, advertising etc) will be submitted to the site Human Ethics Review Committee (HREC) and to regulatory authorities in the countries where the study will be conducted.

Written confirmation of approval (noting version/ date of all approved documents) must be received the Investigator before the study commences and approval of all documents pertaining to this study will be kept in the study Master file.

The HREC will have at all times the right to review all source documentation.

15.2 GOOD CLINICAL PRACTICE

The study will be conducted in accordance with the principles of good clinical practice (GCP) using the guidelines established in 1996 by the International Council on Harmonisation (ICH), annotated in July 2000 by the TGA.

Compliance with these guidelines ensures compliance with the currently approved version of the Declaration of Helsinki (October 2000) with notes of Clarification in 2002 (Washington) and 2004 (Tokyo) and any local legal and regulatory requirements.

15.3 ADHERENCE TO PROTOCOL

No changes or deviations in the conduct of this protocol will be permitted, with the exception of emergency situations. The Investigator should contact the Sponsor by telephone as soon as possible. The nature and reasons for the protocol deviation should be recorded in the CRF.

In the event of an emergency, the Principal Investigators will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Sponsor, the Medical Monitor, and the HREC.

Protocol violations are defined as any deviation from this protocol, and include items such as a study required evaluation not completed according to the protocol, a study visit completed outside of the defined visit window, etc.

A major protocol violation would include, but not be limited to, the following:

- enrolment of a patient who does not meet the inclusion/exclusion criteria.
- enrolment of a patient who has not provided informed consent
- the non-reporting of serious adverse events according to protocol and regulatory requirements

All protocol violations will be reported to the Sponsor via a protocol violation form. Major protocol violations must be reported to the Sponsor as soon as the Investigator or the Data Monitor becomes aware of them.

All major protocol violations will be reported to the Human Research Ethics Committee (HREC) with response and approval required for any change or deviation that may increase risk to the Patient, and/or that may adversely affect the rights of the Patient or validity of the investigation.

15.4 PROTOCOL AMENDMENTS

Amendments to the protocol need to be approved by the Sponsor and the Study Steering Committee. Major amendments will require the approval of the HREC. Minor amendments will require that the HREC be notified. Any amendments affecting the involvement of patients would require all patients being notified.

16 PATIENT INFORMED CONSENT

The patient informed consent form contains the 20 elements required for the provision of informed consent as described in ICH E6(R2) 4.8. in accordance with the Code of Federal Regulations (21 CFR 50.25) and the latest amendment of the Declaration of Helsinki (October 2013). Additionally, the informed consent form has been reviewed and approved by the Sponsor and the study HREC prior to initiation of the study.

The Principal Investigator, or a person designated by the investigator, is responsible to explain the nature of the study and the risks and benefits of taking part to the patient in order to obtain the patent's written consent. It should be stressed that participation is voluntary. The patient can refuse to participate and is free to withdraw from the study at any time, without affecting their future medical management.

Prior to undertaking any study specific activity, the Investigator should explain the nature of the study to the patient, including providing a written information sheet which should be read and retained by the patient. All patients must give fully informed consent, which must be obtained in writing by a personally dated signature and witnessed. The signed consent form should be available to be viewed by the Clinical Study Monitor and a copy of all consent documents provided to the patient.

Patients must be informed that representatives of the Sponsor, HREC and regulatory authorities may inspect their medical records in order to verify the accuracy and authenticity of study documentation including information entered in the eCRF. Patients must be informed as to the nature of the privacy guidelines in place to protect their anonymity.

Any amendments to the Informed Consent Form will need to be approved by the Sponsor and the HREC.

17 DISCLOSURE OF DATA

17.1 CONFIDENTIAL INFORMATION

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted below is prohibited. All patients will be assigned a study identification number.

Patients will be identified on case report forms only by their patient number and initials.

At the patient’s request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection on request by representatives of state and federal health authorities, the Sponsor, and the HREC.

All published information from this study will be presented in such a way that it does not permit identification of individual patients. Patient identity will remain protected except as required by regulatory or legal inquiries.

To fully evaluate patient safety issues that may arise during the study, Sponsor, or state and federal authorities will require direct access to source documents including trial-related monitoring, audits, HREC review and regulatory inspection(s).

It must be explained to the patient before enrolment into the study that the patient's Protected Health Information (PHI) obtained during the study may be shared with the study, Sponsor, state and federal authorities, and HREC regulatory inspections(s).

17.1.1 Study records and source documents

All clinical information obtained by the Investigator is confidential, including that supplied by the Sponsor, and disclosure to third parties must be limited to:

i. Those undertaking legitimate peer review of the scientific and ethical aspects of the study such as, but not limited to, the TGA and/or FDA.
ii. Other staff participating in the study, so that necessary medical care can be undertaken.
iii. The patients, so that written informed consent can be obtained.
iv. Representatives of the sponsor, including the Monitor(s).

Patients will be identified to the sponsor and regulatory authorities only by their study number and initials recorded on the CRF. Other patient details are to be obscured if a document is being forwarded to the Sponsor with the CRF or provided to regulatory authorities for review.

The Investigator will maintain a patient screening and enrolment log (patient numbers and the corresponding patient names) to enable the records to be identified.

17.1.2 Prior to study commencement

Prior to the release of clinical study supplies and the study commences, the following documents will be collected from the Principal Investigator:

i. An up-to-date, signed and dated Curriculum Vitae for all Investigators and other study staff.
ii. The signed Protocol and any amendments.
iii. The signed clinical study agreement (CSA).
iv. The signed letter from the HREC giving approval for the study (version numbers/dates of all approved documents to be included), together with a letter of constitution of the HREC. Copies of any other correspondence with the HREC relevant to the study should also be supplied.
v. The signed letter from the relevant national authority acknowledging the study.
vi. Current laboratory certification of the laboratory(ies) performing analysis, as well as current normal laboratory ranges for all laboratory tests.

The Investigator shall provide to the Sponsor all observations and test results required in the protocol and indicated in the CRFs. In particular, all details of adverse events, as defined in the protocol should be supplied.

17.1.3 Document retention

The Principal Investigator will retain copies of the following documents in a secure place for a period of 15 years from completion of the study per Therapeutic Goods Administration (TGA). These documents may be retained for a longer period by agreement with the Sponsor.

i. A signed copy of the Protocol and any amendments.
ii. Copies of the patients' Case Report Forms and Data Clarification Forms.
iii. The patient informed consent documents.
iv. Copies of the Curricula Vitae of the Investigator and study staff.
v. Copies of all correspondence with the HREC and national regulatory authority.
vi. Copies of relevant laboratory ranges.
vii. Copies of all correspondence to and from the Sponsor and the Monitor and the Investigator.
viii. The patient's original clinical notes.

The Sponsor will provide the Principal Investigator with information concerning the current status of the investigational drug as it relates to the Investigator's obligation for the retention of study records.

The Investigators should contact the Sponsor prior to disposing of any such records. The Sponsor will arrange for continued storage of all records, if necessary and as documented in the Clinical Study Agreement.

The Sponsor will maintain correspondence with the Principal investigator after study closeout to ensure that study documentation is retained for the appropriate amount of time. The investigator must inform the Sponsor immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

In the event the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (e.g., another investigator). Notice of such transfer will be given in writing to the Sponsor.

17.1.4 Access to source documents

To ensure the accuracy of the data collected in the CRFs, representatives from the Sponsor, Regulatory Authorities and the Monitor may require access to source documents (i.e. patient records, patient charts, laboratory reports, X-ray reports and scans). Anonymity of the patient will be maintained at all times.

17.1.5 Publication policy

To avoid disclosures that could jeopardize proprietary rights, Investigators are required to submit all publications to the Sponsor prior to submission to a publisher. The Sponsor will review any such submissions within 30 days of receipt. Permission to publish will not be withheld unreasonably.

Details of the study will be registered prior to commencement at www.clinicaltrials.gov, with information updated throughout the course of the trial. Publication in medical or scientific journals will conform to guidelines set out in the International Committee of Medical Journal Editors (ICMJE)[1],and consult reporting standards such as the CONSORT[2] group and the individual journals.

Available on http://www.icmje.org and on http://www.consort-statement.org

18 ADDITIONAL PATIENT CARE DURING POST-STUDY

18.1 EMERGENCY CONTACT

18.1.1 Investigator

The Principal Investigator, or nominated deputy, will be available for consultation by the patient at any time during the study period. Names and telephone numbers of staff responsible for the study will be made available to the patient. The Investigator must ensure that adequate medical care is provided for any adverse events. The Investigator should inform the patient when medical care is required for any intercurrent illness.

18.1.2 Sponsor

In an emergency, the Principal Investigator should contact both the study Sponsor and the Monitor by telephone.

18.1.3 Liability and Insurance

With effect from the commencement of the study, the Sponsor will indemnify study participants according to the local institutional regulations concerning clinical study involvement.

19 REFERENCES

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20 APPENICIES

20.1 APPENIDIX 1- ECOG SCORE*

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

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am. J. Clin. Oncol. 5:649-655, 1982. Eastern Cooperative Oncology Group, Robert Comis, M.D., Group Chair.

20.2 APPENDIX 2- BPI-SF

Sample of Brief Pain Inventory Short Form Questionnaire

1903

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject's Initials : _____

Study Subject #: ☐☐☐☐

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

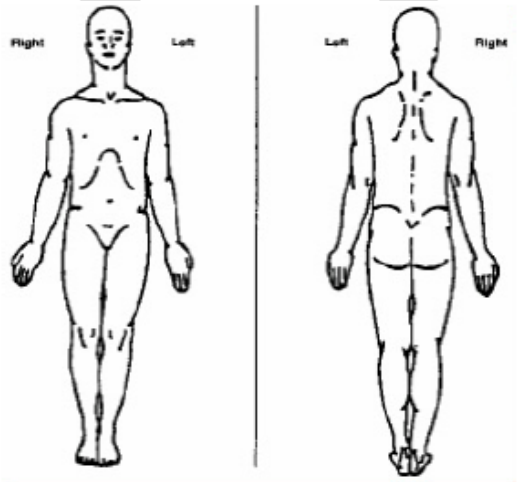
Revision: 07/01/05

Brief Pain Inventory (Short Form)

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 everyday kinds of pain today?

☐ Yes ☐ 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 marking the box beside the 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 marking the box beside the 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 marking the box beside the 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 marking the box beside the 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

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

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 mark the box below the 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. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

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

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

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