2019

NOX66-001A
Protocol Version 3.0

NCT02941523

NOXOPHARM LIMITED

CLINICAL PROTOCOL

Title: Phase Ia/Ib and Potential Phase IIa Study of the Safety and Pharmacokinetics of NOX66 Both as a Monotherapy and in Combination with Carboplatin in Patients with Refractory Solid Tumours

Protocol Number: NOX66-001A

Product: NOX66 (Idronoxil Suppository Formulation)

Sponsor: Noxopharm Limited
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Version: 3.0

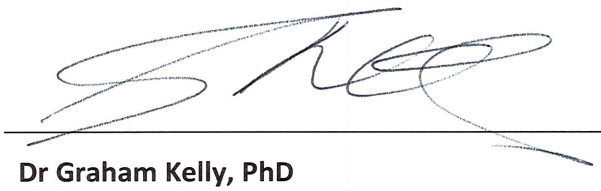
Date: 20th July 2017

CONFIDENTIALITY STATEMENT

SIGNATURES

SPONSOR

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



21/07/17

Dr Graham Kelly, PhD
Chief Executive Officer, Noxopharm Limited

Date

INVESTIGATOR SIGNATURE

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.

PRINCIPAL INVESTIGATOR

Name	**Signature**	**Date**

1 STUDY SYNOPSIS

Name of Company Sponsor	NOXOPHARM LIMITED
Title of Study	Phase Ia/Ib and Potential Phase IIa Study of the Safety and Pharmacokinetics of NOX66 Both as a Monotherapy and in Combination with Carboplatin in Patients with Refractory Solid Tumours
Study Number	NOX66-001A
Development Phase	Phase 1a/1b
Name of Active Ingredient	Idronoxil
Description of Investigational Product	NOX66 is idronoxil formulated as a suppository in a standard suppository base. Each suppository contains 400 mg idronoxil.
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 either 400 mg daily (1 suppository daily) or 800 mg daily (1 suppository twice daily).
Number of Subjects (planned)	For the **Phase Ia and Ib arms** of the Study a total of 16 (evaluable) patients will be recruited and divided into 2 Cohorts of 8 patients each as follows: Cohort 1: 400 mg idronoxil dosage. Cohort 2: 800 mg idronoxil dosage. The maximum number of patients to be recruited in Phase I arms is 22 patients. The **Phase IIa arm** is triggered by an objective response to combination therapy in the Phase Ib arm. For this, 10-12 additional subjects with the same tumour type will be enrolled on the same combination treatment regimen. There will be a maximum number of two (2) such Phase IIa cohorts, each with a maximum of 24 subjects. If Phase IIa proceeds with 2 further cohorts (Cohorts 3 and 4), the total number of patients enrolled in the Study will be 34 -40.
Indication	Solid tumours with no standard therapeutic alternatives.
Study Period and Duration of Treatment	Treatment in the Phase Ia (Run-In) Arm is for 1 Treatment Cycle (14-days treatment followed by 1 week of rest) only. Treatment in the Phase Ib (Combination) Arm is intended to be for a maximum of 6x 28-day Treatment Cycles (total treatment time = 6 months). However,

	combination treatment cycle may continue if the Investigator considers that there is clinical benefit to the subject, and that the benefits outweigh the risks. Treatment in Phase IIa (Combination) Arm is intended to be for a maximum of 6x 28-day Treatment Cycles (total treatment time = 6 months).
Primary Study Objective	• to determine the tolerability, adverse event profile, maximum tolerated dose (MTD), and dose-limiting toxicities (DLTs) of idronoxil in a suppository dosage form (NOX66) in patients with refractory solid tumours, both as a single agent and in combination with carboplatin • to determine if idronoxil in a suppository dosage form (NOX66) is able to combine with a standard dosage of carboplatin to produce a meaningful anti-cancer effect in solid tumours considered to be refractory to cytotoxic chemotherapy • to determine if idronoxil in a suppository dosage form (NOX66) is able to combine with dosage of carboplatin two-thirds of the standard dosage to produce a meaningful anti-cancer effect in solid tumours considered to be refractory to cytotoxic chemotherapy
Secondary Study Objectives	• to characterise some key pharmacokinetic features of idronoxil when administered rectally • to determine if various biomarkers of idronoxil biologic activity have any correlation to the efficacy or toxicity of idronoxil in combination with carboplatin.
Methodology	The Study has 3 separate components - Phase Ia, Phase Ib and a potential Phase IIa component. **The Phase 1a** component will comprise 21-day Run-In Arm of idronoxil monotherapy administered on a two-step dose-escalation basis. Patients to receive idronoxil treatment once or twice (12-hourly) daily for 1 Treatment Cycle only. Cohort 1: 400 mg idronoxil daily. Cohort 2: 800 mg idronoxil daily. In each regimen, treatment is taken daily for 14 consecutive days followed by 7 days of rest, comprising a 21-day Treatment Cycle. Any patient experiencing Dose-Limiting Toxicity (DLT) in Cohort 1 will have their dosage halved to 400 mg idronoxil every 2nd day. Any patient experiencing DLT in Cohort 2 will revert to Cohort 1 treatment regimen. **The Phase Ib** component will comprise idronoxil administered in combination with carboplatin up to 6 Treatment Cycles each of 28-days. All patients completing the Run-In Arm without significant toxicity will be offered combination treatment with carboplatin. Patients will remain in the same Cohort

	(1 or 2) and be treated with idronoxil at the same dosage received in the Run-In Arm and receive the following treatment with carboplatin. Carboplatin Regimen 1: carboplatin AUC = 4 for Treatment Cycles 1-3 Carboplatin Regimen 2: carboplatin AUC = 6 for Treatment Cycles 4-6. Idronoxil to be administered Days 1-7 of each 28-day Treatment Cycle. Carboplatin to be given intravenously on Day 2 of each Treatment Cycle. Note: maximum dose for AUC = 4 is 600 mg and for AUC = 6 is 900 mg. DLT will be managed with a mixture of a reduction in dosage or withholding of idronoxil and/or carboplatin, to be determined in consultation with the Investigator, the Medical Monitor, and the Sponsor **The Phase IIa** component can be triggered by observed meaningful clinical responses from the Phase Ib Arm in particular disease indications and will be activated only with the agreement of the Principal Investigators. The combination treatment of idronoxil + carboplatin will be administered over 6 Treatment Cycles each of 28-days at dosages considered appropriate by mutual agreement between the Sponsor and the Principal Investigators. A maximum of 2 additional patient cohorts, each comprising an additional 10-12 patients with specific disease states can be enrolled.
Criteria for Evaluation	**Safety:** to be assessed through the analysis of routine laboratory tests (haematology, serum chemistry, urinalysis), physical examinations, vital signs, and ECOG status. Adverse event monitoring will be performed and assessed using the CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE) scoring system. **Efficacy:** All efficacy assessments will be performed at the discretion of the Investigator but at a minimum should include a baseline assessment (CT scan, ECOG assessment) and follow-up assessments at a minimum of every 12 weeks while receiving study drug. Tumor response and progression-free survival will be assessed using standard RECIST criteria. **Pharmacokinetics**: blood and 24 hour-urine samples will be analysed to determine the primary idronoxil metabolites and the primary route of excretion. **Biomarkers:** Ceramide and sphingosine-1-phosphate (related to the molecular target of idronoxil) and ENOX2 will be assessed at baseline and at completion of idronoxil therapy per cycle. Biomarker and plasma idronoxil levels to be correlated with anti-cancer activity and any toxicity.
Statistical Methods	Statistical analyses will be primarily descriptive in nature and statistical hypothesis testing will not be performed. All patients will be included in the evaluation of safety. Data will be presented by Cohort, by idronoxil and carboplatin dosages, and by tumour type.
Inclusion Criteria	1. Provision of informed consent. 2. Male or female ≥18 years of age.

	3. Histologic or cytologic confirmed locally advanced or metastatic cancer that has no standard therapeutic alternatives. 4. At least 1 measurable lesion by CT/MRI scan. 5. ECOG Performance status 0-1 (Appendix A). 6. A minimum life expectancy of 12 weeks. 7. 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 8. Female patients who are known to be capable of conception should have a negative serum pregnancy test (beta-human chorionic gonadotropin (β-hCG)) within 1 week of starting the study. 9. All potentially fertile patients will agree to use an effective form of contraception during the study and for 90 days following the last dose of NOX66 (an effective form of contraception is defined as an oral contraceptive or a double barrier method. 10. 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 Grade 1. 11. At least 21 days must have elapsed prior to Day 1 Cycle 1 since radiotherapy (limited palliative radiation is allowed > 2 weeks), immunotherapy or following major surgery and any surgical incision should be completely healed.
Exclusion Criteria	1. Patients who are pregnant or breastfeeding. 2. Tumor involvement of the Central Nervous System (CNS): • Patients with treated and stable CNS metastases may be eligible to participate after discussion and approval from the Medical Monitor. 3. Uncontrolled infection or systemic disease. 4. 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. 5. Patients with QTc of > 470 msec on screening ECG. (If a patient has QTc interval >470 msec on screening ECG, the screening ECG may be repeated twice (at least 24 hours apart). The average QTc from the 3 screening ECGs must be <470 msec in order for the patient to be eligible for the study. 6. Any major surgery, radiotherapy, or immunotherapy within the last 21 days (limited palliative radiation is allowed > 2 weeks).

	7. Chemotherapy regimens with delayed toxicity within the last 4 weeks. Chemotherapy regimens given continuously or on a weekly basis with limited potential or delayed toxicity within the last 2 weeks. 8. Any situation where the use of suppository therapy is contra-indicated or impractical (e.g. chronic diarrhea, colostomy, ulcerative colitis). 9. No concurrent systemic chemotherapy or biologic therapy is allowed. 10. Known human immunodeficiency virus (HIV) or Hepatitis B or C (active, previously treated or both). 11. History of solid organ transplantation. 12. Psychiatric disorder or social or geographic situation that would preclude study participation. 13. Known unsuitability for treatment with carboplatin including renal disease where there is impaired glomerular filtration rate (GFR).

2 LIST OF TABLES

3 LIST OF ABREVIATIONS

Abbreviation/term	Definition
AE	Adverse Event
^{0}C	Degrees Celsius
CBC	Complete Blood Count (otherwise known as FBC)
CFR	Code Federal Regulations
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computerised Tomography
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ENOX2	Tumour-associated NADH oxidase
FDA	Food and Drug Administration
G	Gram(s)
GCP	Good Clinical Practice
Hr	Hour
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
Kg	Kilogram
M	Micro
mM	Micromolar
Mg	Milligram(s)
mL	Milliliter(s)
Min	Minute(s)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI CTC	National Cancer Institute, Common Toxicity Criteria
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class

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4 ROLES AND RESPONSIBILITIES

4.1 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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4.2 INVESTIGATOR AND SITES

No.	**Principal Investigator**	**Site** (Name and Address)
1.	Dr. Lia Abshilava	Medulla-Chemotherapy and Immunotherapy Clinic A.Politkovskaia street #6 Tbilisi, Georgia 0186
2.	Dr. Mikheil Shavdia	JSC “Neo Medi’ Kristine Sharashidze Street #12 Tbilisi, Georgia 0131

4.3 CLINICAL RESEARCH ORGANISATION

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5 INTRODUCTION

5.1 OVERALL AIM

This study forms part of a global program aimed at developing idronoxil (in a suppository dosage formulation) as an adjunct therapy that will:

- increase the efficacy of standard frontline chemotherapies and radiotherapies
- restore sensitivity to those frontline therapies in cancers that have become refractory to standard therapies
- sensitise tumour cells to standard frontline therapies to the extent that their dosages can be lowered to well tolerated levels.

5.2 BACKGROUND

5.2.1 General

As a general statistic, the likelihood of a cancer patient surviving 10-years following diagnosis has doubled from 25% to 50% over the past 45 years. However, for many forms of cancer, 5- and 10-year survival prospects have changed little in that time, with cancers of the pancreas, lung, gall-bladder, head & neck, stomach and brain being obvious examples. But even where patients are living longer, aggressive cancers that have spread beyond their original site invariably return and are fatal.

Chemotherapy and radiotherapy remain the standard frontline therapies for the great majority of patients and for the great majority of tumour types, despite their shortcomings. There have undergone undoubted refinements over the past 45 years, but their underlying function has not changed and their shortcomings and limitations are unchanged. More recent developments such as immunotherapy have failed to dislodge chemotherapy and radiotherapy from their dominant position.

The failure of chemotherapy and radiotherapy to have had a bigger impact on survival prospects is due to 2 factors: first, their general poisoning effect which prevents them from being used at higher and more effective dosages; and, second, the ability of cancer cells to become resistant to both drugs and radiation.

The problem of resistance has been identified as the single largest problem facing better management of cancer. Without this resistance, cancer cells would be killed by much lower levels of chemotherapy or radiotherapy.

This is the objective of the current global NOX66 program is to use its active drug, idronoxil, to remove the ability of the cancer cell to resist chemotherapy and radiotherapy so that dosages of those therapies that currently are providing only partial killing of cancer cells, will effectively kill all cancer cells within the body.

Scientists have identified the main biochemical mechanisms within a cancer cell responsible for this resistance (e.g. PI3 kinase and Akt signalling pathways) and these have become an obvious target for drug development. However, despite considerable effort over the past decade, no drug has proven effective in the clinic because of the inability of the drugs developed to date to distinguish between cancer cells and healthy cells. Signalling pathways such as PI3 kinase and Akt are essential pathways responsible for the survival of all human cells. Shutting them down in cancer cells in order to block the cancer cell's ability to develop resistance mechanisms, comes at the cost of reducing a healthy cell's ability to survive.

Idronoxil is the first drug that selectively inhibits PI3 kinase/Akt in cancer cells, with no known adverse effects on healthy cells. As a result of this, idronoxil in the laboratory (cells and animals) leads to a very high level of sensitisation of all forms of cancer to the killing effects of chemotherapy drugs allowing dosages of those drugs to be reduced >2000-times and still achieve 100% cancer cell killing. This effect on cancer cells is achieved with no increased sensitivity to the same drugs in healthy cells.

Detail of all pre-clinical studies can be found in the IB edition 2.0, section 5.0.

5.2.2 Regulatory Background of Idronoxil

Both oral and intravenous dosage form of idronoxil have been used in over 400 patients in 18 clinical studies in Australia, United States, United Kingdom, Germany, Belgium and Poland between 1999 -2009.

Both dosage forms have been granted Investigational New Drug (IND) status by the United States Food and Drug Agency (FDA). Both dosage forms also have been awarded Orphan Drug Status for the treatment of late-stage ovarian cancer by the FDA.

Both oral and intravenous dosage forms have been approved by the Australian Therapeutics Good Agency (TGA) for use in 8 clinical trials in cancer patients.

Hospitals that have approved the use of idronoxil in patients include:

UK

- Royal Marsden Hospital
- University College London
- Imperial College London

Germany

- Campus Virschow Clinic, University Hospital, Berlin

Belgium

- Katolieke Universiteit Leuven

- Antwerp University Hospital

Poland

- Poznan University of Medical Sciences
- Hollycross Oncology Centre, Kielce

USA

- Yale-New Haven Cancer Center
- Augusta Oncology Associates
- Bennett Cancer Center, Stamford
- Cleveland Clinic

Australia

- Mater Adult Hospital, Brisbane
- Westmead Hospital, Sydney
- Royal North Shore Hospital, Sydney
- St George Hospital, Sydney
- Royal Prince Alfred Hospital, Sydney
- St John of God Hospital, Perth
- Royal Women's Hospital, Melbour

5.3 CLINICAL EXPERIENCE

Eighteen (18) clinical studies (Phase 1, Phase 2, Phase 3) have been conducted with the oral and intravenous dosage forms of idronoxil. With the exception of one Phase 2 study in patients with haematological cancers, all other studies have involved patients with end-stage solid cancers. The primary clinical indication eventually pursued was restoration of sensitivity to carboplatin in late-stage, platinum-refractory ovarian cancer.

The drug has proven to be well tolerated. No bone marrow, hepatic, renal, neurological or cardiac toxicity has been reported or observed in over 400 patients. Fatigue is the only reported monotherapy toxicity at maximum Grade 2 level in <5% patients.

No maximum tolerable dosage level has been determined in humans. The highest dosage that is practically able to be administered is 40 mg/kg on a repeated daily basis, and that is without any toxicity.

Details of each clinical study is available in IB Edition 2.0, section 6.0

5.4 RATIONALE FOR NOX66

Idronoxil has proved to be a highly effective chemo-sensitiser in the laboratory in both in vitro studies and in animal models of human cancers. And while evidence of that anti-cancer effect has been obtained in a number of Phase 2 clinical studies, this anti-cancer effect has been inconsistent and infrequent, falling well short of its pre-clinical promise.

Recent studies now suggest that a previously-unknown mechanism of drug-resistance lies behind this disappointing clinical result, with most tumours in most patients probably possessing an ability to block the effect of idronoxil.

This phenomenon involves Phase 2 metabolism. This is an important detoxification system within the body designed to convert water-insoluble foreign chemicals into water-soluble forms able to be eliminated quickly in the urine. This is a process that idronoxil shares with other drugs such as aspirin, paracetamol, codeine, propofol, naxolone and steroid hormones. What all these drugs have in common is an underlying phenolic chemistry structure, rendering them poorly soluble in water.

The Phase 2 metabolism of phenolic drugs involves two steps. Step A is the attachment by certain enzymes (*transferases*) of a sugar (glucuronic acid) to the drug. This makes the drug more soluble in water, allowing it to be readily transported in blood and readily excreted in urine. In this form, however, the drug is inactive because it is too large to bind to its target.

Activation of the drug is Step B. This involves the removal of the sugar, a step conducted by another family of enzymes (*glucuronidases*) present inside most cells. In Step 2, the drug + sugar complex leaves the bloodstream and enters its target cell where the drug is separated from its attached sugar and now is free to bind to its target within the cell.

Idronoxil undergoes the same process. Following oral or intravenous dosing, 100% of all idronoxil in the bloodstream is subject to Phase 2 metabolism. And in common with all other phenolic drugs, the idronoxil + sugar complex enters a cell, is released from its sugar, and it free to work.

Recent studies, however, have revealed that while normal cells contain the necessary glucuronidase enzymes, the cancer cells that have been studied are lacking in this enzyme activity by as much as 90%. This is assumed to be just another defence mechanism of cancer cells that helps them avoid chemotherapy.

This means that the great majority of idronoxil that reaches the cancer cell remains attached to its sugar and unable to work.

NOX66 has been developed to lessen the ability of the body to attach glucuronic acid to idronoxil so that the drug remains as much as possible in a (sugarless) form that retains is anti-cancer activity. In this way, the drug is not required to enter the cancer cell to have its attached sugar

removed and therefore is unaffected by the cancer cell's ability to develop multiple drug resistance mechanisms.

The rationale is to administer idronoxil rectally. This is intended to minimise Phase 2 metabolism in 2 ways:

- first, the transferase enzymes that provide frontline Phase 2 metabolism and which occur in the lining of the gut from the stomach down to the large bowel, are absent in the lining of the rectum
- second, that venous drainage from the lower half of the rectum is via the inferior vena cava, thus avoiding first pass liver metabolism.

Collectively these 2 anatomical features are intended to minimise the degree of exposure of idronoxil to Phase 2 metabolism.

Studies in rats have confirmed this rationale. Delivering idronoxil rectally as NOX66 reduces the degree of Phase 2 metabolism of idronoxil in rats by 90% compared to oral dosing, leaving a significant proportion of idronoxil circulating within the bloodstream in a non-detoxified form.

5.5 SUPPOSITORIES – STANDARD THERAPY

Many drugs are given both orally and rectally. Rectal administration generally is used for 3 reasons:

1. Where the patient is suffering nausea or where the drug may be irritant to the stomach;
2. Where fast action is required (absorption generally very rapid from the rectum);
3. Where it is considered desirable to avoid Phase 2 metabolism in the liver.

Point 3 above is part of the rationale for NOX66. Phase 2 metabolism takes place both in the lining of the gut and in the liver. Drugs absorbed rectally avoid first pass liver metabolism, substantially reducing their exposure to the liver's detoxification enzymes.

NOX66 consists of idronoxil contained in a standard (commercial) fatty base used in the manufacture of a wide range of suppositories.

5.6 POTENTIAL RISKS

No potential risks are anticipated from the use of idronoxil in this Study based on:

- idronoxil specifically attaches to a target that is only present on tumour cells
- laboratory studies have failed to find any toxicity of idronoxil towards normal cells

- animal studies with oral or intravenous dosage formulations have been unable to determine the maximum tolerated dose
- in a Phase 3 clinical study when given orally on a continuous daily basis over a 21-day period (at a dosage more than double the highest proposed dosage in this study) in combination with a standard dose of carboplatin, there was no toxicity > Grade 2.

The administration of idronoxil as NOX66 is not expected to lead to a safety profile any different to that of the previously-used oral dosage form. Despite the Phase 2 metabolism of orally administered idronoxil, the drug still was activated within normal cells. For that reason, the effect of idronoxil on normal cells is predicted to be exactly the same whether given orally or rectally, and whether subjected to complete or incomplete Phase 2 metabolism.

It should also be noted that this is a limited, two-step dose-escalation study of 400 and 800 mg idronoxil daily. Patients are to be closely monitored for safety by physical exam, hematologic and chemistry evaluations, urinalysis, and ECG analyses. Any evidence of toxicity is expected to be noted early and the dosage of NOX66 adjusted if necessary.

6 STUDY OBJECTIVES

6.1 PRIMARY OBJECTIVES

- to determine the tolerability, adverse event profile, maximum tolerated dose (MTD), and dose-limiting toxicities (DLTs) of idronoxil in a suppository dosage form (NOX66) in patients with refractory solid tumours, both as a single agent and in combination with carboplatin
- to determine if idronoxil in a suppository dosage form (NOX66) is able to combine with a standard dosage of carboplatin to produce a meaningful anti-cancer effect in solid tumours considered to be refractory to cytotoxic chemotherapy
- to determine if idronoxil in a suppository dosage form (NOX66) is able to combine with dosage of carboplatin two-thirds of the standard dosage to produce a meaningful anti-cancer effect in solid tumours considered to be refractory to cytotoxic chemotherapy.

6.2 SECONDARY OBJECTIVES

- to characterise some key pharmacokinetic features of idronoxil when administered rectally
- to determine if various biomarkers of idronoxil biologic activity have any correlation to the efficacy or toxicity of idronoxil in combination with carboplatin.

7 STUDY DESIGN

This is a Phase I, open-label, non-randomized, dose-escalation (two-step) study of experimental drug, idronoxil, in a suppository dosage formulation (NOX66) in patients with refractory solid tumours that have stopped responding to standard treatment options.

The patients will have solid cancers selected from 5 phenotypes: prostate, breast, ovarian, lung, head and neck.

The study has two confirmed arms: a Phase Ia (Run-In) Arm where idronoxil is used alone and a Phase Ib (Combination) Arm where idronoxil is used in combination with carboplatin.

A Phase IIa arm is a potential third arm. This will only be triggered by clinical responses in the Phase Ib arm that are considered by the Investigators to be meaningful.

Sixteen (16) patients will be recruited and 8 patients allocated to each of two cohorts – Cohort 1 and Cohort 2. Cohort 1 will receive an idronoxil dosage of 400 mg daily; Cohort 2, 800 mg daily. Recruitment into Cohort 2 will not occur until at least 7/8 Cohort 1 patients have completed at least 1 Phase Ia Treatment Cycle without Dose-limiting Toxicity (DLT).

7.1 Phase I Arm

In the **Phase Ia (Run-In) Arm**, patients will self-administer idronoxil rectally either once or twice (12-hourly) daily for 14 consecutive days for one (21-day) Treatment Cycle using one of 2 idronoxil dosages.

The main purpose of the Phase Ia Arm is to confirm the tolerability of idronoxil (in the NOX66 dosage formulation) when used as a monotherapy over an extended period of treatment (14 consecutive days).

The **Phase Ib (Combination) Arm** will commence immediately following the Phase Ia (Run-In) Arm and will comprise idronoxil being administered in combination with carboplatin. Patients will remain in the same two starting cohorts and remain on the same idronoxil dosage.

Within each 28-day combination treatment cycle, idronoxil treatment will commence on Day 1 and continue daily for 7 consecutive days; carboplatin will be administered intravenously on Day 2.

There will be two different dosages of carboplatin administered: AUC = 4 and AUC = 6. Patients will start with the lower dose and receive that for 3 Treatment Cycles. Providing there is no DLT, patients then will progress onto the higher dosage of carboplatin which they will receive for up to a further 3 Treatment Cycles.

The primary aim of this phase is to see if idronoxil can induce a meaningful clinical response (complete or partial remission by RECIST) in combination with carboplatin in cancers that have stopped responding to standard chemotherapy and generally would be considered unlikely to respond to further standard therapy. And then further, to see if this meaningful combination anti-cancer effect is possible with a dosage of carboplatin that would be regarded generally as being well tolerated but unlikely to deliver a significant anti-cancer effect.

7.2 Phase II Arm

The **Phase IIa Arm** can commence providing that a meaningful clinical response (partial or complete tumour response as determined by RECIST criteria) has occurred in some patients in the Phase Ib Arm. Up to a maximum of 12 patients can be recruited of similar tumour type and disease status as the Phase Ib patients showing the clinical response and form the basis of 2 new patient cohorts.

8 STUDY PARTICIPANTS

8.1 STUDY POPULATION

Patients with refractory solid tumors that have failed standard treatment options.

8.2 INCLUSION CRITERIA

Patients must fulfill all of the following inclusion criteria to be eligible to enroll into the study:

1. Provision of informed consent.
2. Male or female ≥18 years of age.
3. Histologic or cytologic confirmed locally advanced or metastatic cancer that has no standard therapeutic alternatives.
4. At least 1 measurable lesion by CT/MRI scan.
5. ECOG Performance status 0-1 (Appendix A).
6. A minimum life expectancy of 12 weeks.
7. 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
8. Female patients who are known to be capable of conception should have a negative serum pregnancy test (beta-human chorionic gonadotropin (β-hCG)) within 1 week of starting the study.
9. All potentially fertile patients will agree to use an effective form of contraception during the study and for 90 days following the last dose of NOX66 (an effective form of contraception is defined as an oral contraceptive or a double barrier method.
10. 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 Grade 1.

11. At least 21 days must have elapsed prior to Day 1 Cycle 1 since radiotherapy (limited palliative radiation is allowed > 2 weeks), immunotherapy or 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. Patients who are pregnant or breastfeeding.
2. Tumor involvement of the Central Nervous System (CNS):
    - Patients with treated and stable CNS metastases may be eligible to participate after discussion and approval from the Medical Monitor.
3. Uncontrolled infection or systemic disease.
4. 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.
5. Patients with QTc of > 470 msec on screening ECG. (If a patient has QTc interval >470 msec on screening ECG, the screening ECG may be repeated twice (at least 24 hours apart). The average QTc from the 3 screening ECGs must be <470 msec in order for the patient to be eligible for the study.
6. Any major surgery, radiotherapy, or immunotherapy within the last 21 days (limited palliative radiation is allowed > 2 weeks).
7. Chemotherapy regimens with delayed toxicity within the last 4 weeks. Chemotherapy regimens given continuously or on a weekly basis with limited potential or delayed toxicity within the last 2 weeks.
8. Any situation where the use of suppository therapy is contra-indicated or impractical (eg. chronic diarrhea, colostomy, ulcerative colitis).
9. No concurrent systemic chemotherapy or biologic therapy is allowed.
10. Known human immunodeficiency virus (HIV) or Hepatitis B or C (active, previously treated or both).
11. History of solid organ transplantation.
12. Psychiatric disorder or social or geographic situation that would preclude study participation.

13. Known unsuitability for treatment with carboplatin including renal disease where there is impaired glomerular filtration rate (GFR).

8.4 STUDY WITHDRAWRAL

It is planned that all enrolled patients will complete 1 treatment cycle at their assigned dose level. The patient can continue on idronoxil treatment at their allocated dose level weekly after Cycle 1 until demonstrated progressive disease according to Investigator's judgement, or a study withdrawal criterion is met.

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 NOX66;
- a DLT as defined in Section 10.1.4;
- an adverse event related to idronoxil 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 therapy, and, if so, this must be reported in accordance with the procedures in Section 14.2.

8.5 PATIENT REPLACEMENT

Patients who cannot be evaluated as part of the efficacy analysis may be replaced in the study up to total of 16 evaluable patients.

Replacement will occur at end of all safety cohort assessments and patient may be enrolled at the highest tolerated dose level, commencing with treatment cycle 1 of Phase 1b.

9 STUDY MATERIALS

9.1 INVESTIGATIONAL STUDY PRODUCT

9.1.1 Description and Formulation

The drug substance, idronoxil, is manufactured by chemical synthesis and is produced as a single monomer. Idronoxil is manufactured to c-GMP (< 99% purity) specifications.

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 standard (commercial) fatty acid base (MBK®) to yield suppositories with an approximate weight of 2.2 gm and containing 400 mg drug substance. MBK® is a common suppository base for a wide range of marketed drugs and the methods of manufacture, moulding, lubrication and packaging are standard.

9.1.2 Presentation, Storage and Handling

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

NOX66 suppository product will be provided directly by Noxopharm Ltd, the Sponsor.

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

NOX66 suppository is not expected to pose any significant 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

NOX66 suppository is presented in plastic sleeves in boxes. Each box contains 15 suppositories intended to provide 14 single doses, plus 1 spare dose.

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 suppository study product will be provided directly by Noxopharm Ltd, the Sponsor.

Patients are to be given the requisite number of boxes of suppositories on Day 1 of the Treatment Cycle. Patients to return previously dispensed boxes at following visit for in-clinic administration and accountability.

The number of boxes of study product (NOX66) to be dispensed will vary with the NOX66 Treatment Regimen as shown in Table 1.

Table 1. Number of Boxes of NOX66 to be Dispensed per Treatment Regimen

Idronoxil cohort	Run-In Arm No. of boxes	Combination Arm No. of boxes
Cohort 1	1	1 per 2 cycles
Cohort 2	2	1 per cycle

9.2 INVESTIGATIONAL PRODUCT ADMINISTRATION

NOX66 suppository will be self-administered rectally either once or twice daily.

Patients will be provided with 'Instructions for the Use of a Suppository' for reference.

9.3 DURATION OF STUDY TREATMENT

Patients can continue to receive combination therapy of idronoxil and carboplatin at their allocated dose level for:

- up to 6 (six) 28-day treatment cycles OR
- until demonstrated radiologic and/or clinically assessed progressive disease OR
- until another withdrawal criterion is met (See Section 7.4).

9.4 TREATMENT DOSE MODIFICATIONS

There will be no dose modification of idronoxil on the basis of body weight except where the patient exceeds 100 kg body weight in which case the dose of idronoxil may be increased (up to double) at the discretion of the investigator.

If a patient experiences a ≥ Grade 3 adverse event assessed as causally associated with idronoxil during the Run-In phase, the patient should be withdrawn from the study. If a patient experiences a ≥ Grade 3 adverse event assessed as causally associated with idronoxil during the Combination Arm, the patient may continue on idronoxil treatment at their assigned dose provided:

1) the adverse event has resolved to no more than Grade 2 by the time of commencement of the next Treatment Cycle;
2) a treatment break of > 2 weeks due to an unresolved adverse event will require discontinuation of study treatment.

9.5 ACCOUNATBILITY FOR CLINICAL SUPPLIES

The Principal Investigator 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 the Investigator will destroy NOX66 suppositories 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 suppositories to be used other than as directed by this protocol.

9.6 CONCOMITANT MEDICATION

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, but this again is to be confirmed with the Sponsor medical monitor prior to enrolment in the Study.

Patients are not permitted any other experimental drugs treatments.

Supportive care measures and symptomatic treatment for symptom control or drug-related toxicity are permitted including analgesics, etc. Erythropoiesis-Stimulating Agents (ESAs) are permitted but other hematopoietic growth factors are not. Although prophylactic anti-emetics and anti-diarrhoeals (eg. loperamide) are not permitted, they will be allowed if the patient experiences nausea, vomiting or diarrhoea.

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 CRF 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 CRF at each patient visit. "All medications" should include prescription, over-the-counter (OTC) medications, dietary/nutritional supplements, and herbal products.

10 STUDY PROCEDURES AND VISITS SCHEDULE

The following section contains a detailed description of all study visits and procedures.

10.1 STUDY ARMS

10.1.1 Phase Ia (Run-in) Arm

Sixteen (16) patients will be enrolled; 8 patients to be allocated to each of two Cohorts and administered idronoxil (NOX66 suppository) using a 2-step inter-patient dose escalation. There is no intra-cohort dose escalation. Table 2 shows the dosing schedule in terms of NOX66 product and the equivalent dosage of idronoxil.

Table 2. NOX66/Idronoxil Dose Level Schema

Treatment Regimen/ Cohort	NOX66 Dosage	Daily Idronoxil Dosage
1	One suppository, once daily	400 mg
2	One suppository, twice daily (12-hourly)	800 mg

Patients remain on the same daily dosage of idronoxil throughout all arms of the Study.

Idronoxil will be administered over a 21-day Treatment Cycle comprising daily NOX66 administration for 14 consecutive days followed by 7 days of rest.

Once Cohort 1 has enrolled 4 patients, further recruitment to that cohort will be suspended until the fourth evaluable patient completes 1 Treatment Cycle (including the 7-day rest period) and at least 3 of the 4 patients have not experienced any toxicity > Grade 2. The remaining 4 patients in Cohort 1 may then be recruited and start treatment.

Cohort 2 patients may commence idronoxil treatment once all 8 Cohort 1 patients have completed 1 (21-day) Treatment Cycle and at least 6 of those patients have not experienced any toxicity > Grade 2.

Where MTD is deemed to have been reached, up to 6 additional patients may be recruited into the particular cohort in order to confirm the tolerability of the MTD. However, it is not expected that MTD will be reached in this study.

Table 3. Dose escalation Decision Rules for Run-In Arm

Number of patients with toxicity > Grade 2 (or DLT) at a given dose level during the Run-In Arm	Escalation decision rules
0 out of 4	Remaining 4 patients in that cohort to be enrolled and to receive that dose level.
2 out of 8	Remaining 6 patients in that cohort to complete the Run-In phase and proceed to the Combination phase. Next cohort of patients may commence at the higher dose level
1 out of 34	• Enter at least 2 more patients at this dose level • If no further patients experience toxicity > Grade 2, patients to complete the Run-In Arm and proceed to the Combination Arm. Next cohort of patients may commence at the higher dose level. • If 1 or more of this group experience > Grade 2 toxicity (2 of 8 dosed at this group), then dose escalation is stopped and this dose declared the maximally administered dose. Two (2) to 3 additional patients will be entered at the prior lower dose level if only 3 patients were treated previously at that dose.
≥ 2 out of 4	Dose escalation will be stopped. This dose level will be declared the maximally administered dose. Two (2) to 3 additional patients will be entered at the prior lower dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 additional patients at highest dose level below the maximally administered dose	This dose is the MTD and is generally the recommended dose to be used in Phase 2 clinical trials. At least 6 patients must be entered at this dose. Note – this is only applicable if DLTs are experienced in the study in order to determine the MTD.

In the event of toxicity > Grade 2 in any Cohort 1 patient, the idronoxil dosage will be halved by reducing the dosage to 1 NOX66 suppository every second day. If toxicity > Grade 2 persists, the patient will be removed from the Study.

In the event of toxicity > Grade 2 with Idronoxil in any Cohort 2 patient and where the Investigator is confident that the toxicity is related to Idronoxil, the patient will revert to the lower dosage form and will remain at that dosage level for the completion of the 14-day Run-In period of treatment and will stay on that dosage level in the Combination Arm of the study. If toxicity > Grade 2 persists, the patient will be removed from the Study.

10.1.2 Phase Ib (Combination) Arm

As each patient completes 1 Treatment Cycle of the Run-In Arm, they will be offered the combination treatment and may commence that combination treatment immediately providing

that there is no residual toxicity > Grade 1 or in the opinion of the Investigator has recovered from any Study-associated toxicity. Each patient will receive the same idronoxil dosage as they received in the Run-In Arm. A Treatment Cycle is 28-days.

Idronoxil treatment will be daily for 7 consecutive days, commencing on Day 1 and continuing until Day 7.

Carboplatin treatment will be administered intravenously on Day 2 of the Treatment Cycle, starting with a carboplatin dosage of AUC=4 for the initial 3 Treatment Cycles, before proceeding to an AUC=6 for up to 3 remaining Treatment Cycles.

The maximum dosage of carboplatin that may be administered per Treatment Cycle is 600 mg (AUC=4) and 900 mg (AUC=6).

Patients can receive up to 6 treatment cycles of combination therapy at the discretion of the Investigator provided that the patient is not experiencing DLT and the patient, in the opinion of the Investigator, is not experiencing disease progression.

DLT during the Combination Arm of the Study will be managed as a result of discussion between the Investigator, the Medical Monitor and the Sponsor and could involve withholding of idronoxil and/or carboplatin until the patient recovers, and/or a reduction in the dosage of idronoxil and/or carboplatin through a change to a lower idronoxil and/or carboplatin dosage.

If DLT recurs on re-introduction of treatment, the future of that patient is to be discussed with the Medical Monitor.

If a second patient develops a DLT within any treatment regimen, then dose escalation will cease and the prior dose level will be declared the MTD for the combination therapy.

10.1.3 Phase IIa Arm

This Arm can be activated where, in the opinion of the Principal Investigators and the Sponsor, sufficiently meaningful clinical responses have occurred in the Phase Ib Arm of the Study to warrant additional patient enrolment.

There will be a maximum of 2 additional cohorts. Each cohort will comprise up to an additional 10-12 patients with a specific form of cancer. The nature of these 2 additional Phase IIa cohorts will be determined by agreement between the Principal Investigators and the Sponsor.

Patients will be treated with a combination of idronoxil and carboplatin using one of the same treatment schedules as used in the Phase Ib Arm of the Study. Which of the 4 idronoxil/carboplatin dosage combinations that forms the Phase Ib Arm dosage matrix to be used in the Phase IIa Arm, is something that will be determined by agreement between the Principal

Investigators and the Sponsor.

Patients will receive treatment for a maximum of 6 Treatment Cycles provided that the patient is not experiencing DLT and the patient, in the opinion of the Investigator, is not experiencing disease progression.

Patients will be followed for safety and tolerability, and will be monitored and assessed by laboratory testing values as outlined in Section 10.2.

10.1.4 Definition and Determination of Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD).

The Maximum Tolerated Dose (MTD) of idronoxil as a monotherapy in the Phase Ia Run-In Arm will be defined as the dose level immediately below the dose level at which 2 of the first 4 patients per cohort (or at least 3 of 8 patients) during the first cycle of that particular Treatment Regimen experience DLT (related to therapy). Additional patients will be recruited so that at least 6 patients are treated at the designated MTD, with no more than 1 DLT observed among the 6 patients. The MTD will be defined in terms of NCI-CTC graded toxicity during the patients' treatment cycle (21 days).

A dose limiting toxicity (DLT) will be defined as any one of the following occurring during the first treatment cycle 1:

- NCI-CTCAE ≥ Grade 3 neutropenia lasting ≥ 5 days OR febrile neutropenia (fever ≥ 38.5^{o}C) Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding;
- NCI-CTCAE ≥ Grade 3 abnormal laboratory values (except neutropenia and thrombocytopenia) that are assessed as clinically significant and causally associated with NOX66;
- NCI-CTCAE ≥ Grade 3 non-laboratory toxicity that is assessed as causally associated with NOX66; (excluding alopecia, rash, nausea, diarrhea, and vomiting if controlled with standard supportive therapy);

Once any DLT is reported, at least two more patients will be enrolled at the same dose level. Escalation will continue only if a DLT is limited to one of 4 patients. If a DLT occurs in 2 or more patients, further dose escalation will cease and the MTD will be the next lower level.

10.2 CLINICAL AND LABORATORY ASSESSMENTS

10.2.1 Demographic and Other

A medical history will be obtained at screening. Medical history will include demographic data (e.g., date of birth, race/ethnicity). In addition, medical information will be recorded, 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.

10.2.2 Safety

The safety and tolerability of idronoxil will be assessed by monitoring and evaluation of clinical laboratory investigations as below:

- Physical examination, inclusive of Eastern Cooperative Oncology Group (ECOG) performance status.
- Vital signs including height (screening only), weight, standing and supine blood pressure, resting pulse rate, body temperature and respiratory rate.
- Complete Blood Count (CBC) and Chemistry including: white blood cells with differentials, red blood cells, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, sodium, potassium, calcium, creatinine, total protein, albumin, bilirubin (total, direct), AST/SGOT, ALT/SGPT, alkaline phosphatase (ALP); urinalysis (dipstick). Urine microscopy will be performed if urinalysis values are out of range and the investigator deems that the microscopy is clinically warranted.

  Non-fasting samples for clinical laboratory analysis will be collected by a qualified staff member
- 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.
- Blood-based pregnancy tests will be performed on female subjects at Screening and End of Study visit
- Adverse event (AE) monitoring using the National Cancer Institute Common Terminology Criteria for Adverse Events.

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

10.2.3 Pharmacokinetic and Biomarker

Idronoxil levels will be assayed both in plasma samples and 24-hour urine samples collected from patients in both the Phase Ia and Phase Ib Arms of the Study. See section 10.4.6.

Biomarkers (ceramide, sphingosine kinase and ENOX 2 levels) will be measured in the same plasma samples collected for pharmacokinetic analysis. See section 10.4.7.

Plasma collection and 24-hour urine collection procedures are outlined in APPENDIX B.

Idronoxil and biomarker assays will be undertaken by the Sponsor performed by a designated laboratory.

10.3 ASSESSMENT OF DISEASE STATUS

Disease status will be assessed by standard RECIST criteria and ECOG Score. Objective responses will be recorded and reported.

10.3.1 Radiologic Assessments

Baseline radiology by CT or MRI **with contrast** should be performed as close as possible to the start of treatment, but no longer than 28 days (4 weeks) prior to Cycle 1, Day 1. For the purposes of this study patients should be re-evaluated at the Investigator's discretion, but at a minimum of every 12 weeks. The radiologic images should be performed consistently for the areas of disease involvement taken for the study evaluation. If the patient has achieved an Objective Response, a confirmatory scan will need to be performed 4 weeks after the response has been noted per RECIST criteria.

Only those patients who have measurable disease at baseline, have received at least one Phase Ib cycle (28 days) of therapy, and have had their disease re-evaluated will be evaluable for response. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable).

10.3.2 Assessment of Response in Patients with Measurable Disease

Assessments of disease response and progression should be made according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al., 2009).

10.4 STUDY VISITS

10.4.1 Screening

The purpose and the procedures of the study will be fully explained to participants at the screening visit by the Principal Investigator and support staff and every patient approached regarding the study will be provided with the Informed Consent Form (ICF). Patients wishing to enroll in the study will sign the ICF prior to initiating any study related investigations or procedures. Radiological scans performed prior to consent can 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.

All screened patients who sign the informed consent form (ICF) must be recorded on the Screening/Enrollment Log. If a subject who signs an ICF is not enrolled in the study, please provide the reason for exclusion on the log. The Screening/Enrollment Log will be retained within the Investigator Site File.

The screening visit should occur at least 7 days before the commencement of NOX66 treatment. The following procedures are to be performed at the screening visit:

- Review and sign Informed Consent Form
- Review Inclusion and Exclusion Criteria
- Review and record medical history including previous anti-cancer therapy
- Physical examination
- Determination of ECOG performance status (APPENDIX A)
- Vital signs
- 12-lead ECGs will be taken in triplicate, within 5 minutes of each other (over 15 minutes)
- Complete Blood Count
- Serum β-hCG pregnancy test (if female is of child bearing potential)
- Review and record all concomitant medications
- Tumor imaging (CT or MRI), including area of disease involvement. Note: tumor imaging may be performed anytime within 28 days of Cycle 1 Day 1

Table 4. Schedule of Assessments – SCREENING

Obtain Informed Consent	X
Review Inclusion/Exclusion Criteria	X
Medical History	X
Physical Examination (PE)	X
12 Lead ECG	X
ECOG Performance Status	X
Vital Signs	X
Clinical laboratory tests	
Complete Blood Count (CBC)	X
Serum chemistry	X
Pregnancy test (if applicable)	X
Urinalysis (dipstick)	X
Concomitant medication review	X
Tumour imaging	X

10.4.2 Phase Ia (Run-In) Arm Schedule of Procedures

The procedures in this arm of the Study are summarized in Table 5.

Table 5. Schedule of Assessments -Phase Ia (Run-In) Arm

Study Day	**1**	**8**[8]	**15**	**21**[9]
Physical Examination (PE)	X	X	X	
12 Lead ECG [1]	X	X	X	
Vital Signs [2]	X	X	X	
Clinical laboratory tests				
Complete Blood Count (CBC) [3]	X	X	X	
Serum chemistry [3]	X	X	X	
Urinalysis (dipstick) [3]	X	X	X	
Concomitant medication review	X	X	X	X
PK /Biomarker sampling	X[4]	X[5]	X[6]	
Urine collection [7]	X	X	X	
Adverse events/toxicity assessment	X	X	X	X
Dispense study drug	X		X	

[1] ECG conducted 1-hour post NOX66 dosing on Days 1 and 8; any time Day 15.
[2] Vital signs = blood pressure, pulse, respiratory rate and body temperature.
[3] See Section 6.4 for list of blood tests.
[4] Plasma for PK analysis to be collected (Day 1) at t = 0, 30 min, 1 hr and 2 hr post-dosing.
[5] Plasma for PK analysis to be collected (Day 8) at t = 0, 1 hr and 2 hr post-dosing.
[6] Plasma for PK analysis to be collected (Day 15) at 24 hr post-dosing.
[7] 24-hr urine sample to be collected starting from the time of NOX66 dosing on Day 1.
[8] Return study drug for in-clinic administration
[9] Phone call to confirm dose level and continuation to Phase1b.

10.4.3 Phase Ib (Combination) Arm and End of Study Schedule of Procedures

The procedures in this arm of the Study are summarized in Table 6.

Table 6. Schedule of Assessments -Phase Ib (Combination) Arm

	Commencing Treatment Cycle				**Second and subsequent treatment cycles**				
Study Day [1]	**1**[2]	**2**[3]	**7**[4]	**15**	**1**	**2**	**7**	**15**	**End of Study**[9]
Physical Examination (PE)		X	X	X	X	X	X	X	X
12 Lead ECG [5]		X	X			X			X
ECOG Performance Status		X	X	X			X	X	X
Vital Signs [6]		X	X	X	X	X	X	X	X
Clinical laboratory tests									
Complete Blood Count (CBC)		X	X	X	X		X	X	X
Serum chemistry		X	X	X	X		X	X	X
Pregnancy test (if applicable)									X
Concomitant medication review		X	X	X	X	X	X	X	X
Tumour imaging [7]									
PK/Biomarker sampling [8]			X				X		
Adverse events/toxicity assessment		X	X	X	X	X	X	X	X
Dispense study drug	X				X				

[1] There is ± 1-day window allowable for each clinic visit.
[2] Day 1: Commence NOX66 treatment
[3] Day 2: Return study drug for in-clinic administration; Carboplatin treatment 1-hour post-NOX66 administration;
[4] Day 7: Return study drug for in-clinic administration and conclude NOX66 treatment
[5] ECG 1-hour post-NOX66 administration
[6] Vital signs: = weight, blood pressure, pulse, respiratory rate and body temperature.
[7] Tumor burden to be assessed by CT/MRI according to the Investigator's judgement at minimum every 12 weeks. Confirm objective response in 4 weeks.
[8] See Section 10.4.6 - 10.4.7 for the timing of collection of blood and urine for PK and blood for biomarker analyses.
[9] +28 – 33 days after last dose of Carboplatin treatment

10.4.4 NOX66 Dosing Schedules

Table 7. Schedule of NOX66 Treatment in Phase Ia (Run-In) Arm

Study Day	**1-7**	**8-14**	**15-21**
NOX66	X	X	Rest

Table 8. Schedule of NOX66 Treatment in Phase Ib (Combination) Arm per Cycle

Study Day	**1**	**2**	**3-7**	**8-28**
NOX66	X	X	X	Rest
Carboplatin	Rest	X	Rest	Rest

10.4.5 Phase IIa Arm Schedule of Procedures

The procedures in this arm of the Study are summarized in Table 9.

Table 9. Schedule of Assessments - Phase IIa Arm

	Commencing Treatment Cycle				**Second and subsequent treatment cycles**				
Study Day [1]	**1**[2]	**2**[3]	**7**[4]	**15**	**1**	**2**	**7**	**15**	**End of Study**[9]
Physical Examination (PE)	X	X	X	X	X	X	X	X	X
12 Lead ECG [5]			X			X			X
ECOG Performance Status	X		X	X			X	X	X
Vital Signs [6]	X	X	X	X	X	X	X	X	X
Clinical laboratory tests									
Complete Blood Count (CBC)	X		X	X	X		X	X	X
Serum chemistry	X		X	X	X		X	X	X
Pregnancy test (if applicable)									X
Concomitant medication review	X	X	X	X	X	X	X	X	X
Tumour imaging [7]									
Biomarker sampling [8]			X				X		
Adverse events/toxicity assessment	X	X	X	X	X	X	X	X	X
Dispense study drug	X				X				

[1] There is ± 1-day window allowable for each clinic visit.
[2] Day 1: Commence NOX66 treatment
[3] Day 2: Carboplatin treatment 1-hour post-NOX66 administration
[4] Day 7: Conclude NOX66 treatment
[5] ECG 1-hour post-NOX66 administration
[6] Vital signs: = weight, blood pressure, pulse, respiratory rate and body temperature.
[7] Tumor burden to be assessed by CT/MRI according to the Investigator's judgement at minimum every 12 weeks. Confirm objective response in 4 weeks.
[8] See Section 10.4.7 for the timing of collection of blood for biomarker analyses.
[9] +28 – 33 days after last dose of Carboplatin treatment

10.4.6 Pharmacokinetic Analysis

Phase Ia (Run-In) Arm: All patients in the Phase Ia (Run-In) Arm will have plasma and urine analyses conducted over the 21-day treatment cycle.

Blood to be collected on Days 1, 8 and 15 at the following times (Table 10):

Table 10. PK Blood Sampling Schedule for Phase Ia (Run-In) Arm

Day	Sampling time in relation to NOX66 administration
1	t = 0 (pre-dose), then 0.5, 1, and 2 hr post-dose*
8	t = 0 (pre-dose), then 1 hr and 2 hr post-dose*
15	t = 24 hr post-dose

*Post dosing sampling may be taken following administration of the first suppository for Cohort 2 patients.

24-hour urine will be collected on Days 1, 8 and 15, commencing from the time of NOX66 administration on those days and returned at following visit day.

Phase Ib (Combination) Arm: Blood samples to be collected from all patients on Day 7 of each Treatment Cycle at t = 1hour post-dosing. Post dosing sampling may be taken following administration of the first suppository for Cohort 2 patients.

10.4.7 Biomarker Analysis

Blood for biomarker analysis will be collected at the following times:

Phase Ia (Run-In): sample collected from all patients on Days 1, 8 and 15 as follows:

Table 11. Biomarker Blood Sampling Schedule for Phase Ia (Run-In) Arm

Day	Sampling time in relation to NOX66 administration
1	t = 0 (pre-dose), then 1 hr post-dose*
8	t = 1 hr post-dose*
15	t = 24 hr post-dose

*Post dosing sampling may be taken following administration of the first suppository for Cohort 2 patients.

Phase Ib: sample collected from all patients on Day 7 of each cycle, 1hour post dose. Post dosing sampling may be taken following administration of the first suppository for Cohort 2 patients.

11 METHODS OF ASSIGNMENT OF INTERVENTION

11.1 ALLOCATION OF TREATMENT

NOX66-001A is a Phase I open-label, non-randomized, dose-escalation study of idronoxil in suppository form. Patients will be consented, screened and identified as eligible for the study by the Investigator at each site. Eligible patients will be allocated a number for identification on the electronic Case Report Form (eCRF) and for patient tracking purposes. The patients' ID will be determined by a one-digit site number, plus a two-digit patient number, which will be allocated chronologically and will be site specific e.g. first patient at site 1 will be number: 1-01, then sequentially 1-02, 1-03 etc. Likewise, site 2 first patient would be 2-01, 2-02, etc. Study numbers will only be used once and will not be reallocated to any other patient during the study.

Patients should begin protocol treatment within 72 hours of enrollment. Issues that would cause treatment delays longer than 72 hours should be discussed with the Sponsor. If a patient does not proceed to receive protocol therapy following enrollment, the patient's study enrollment may be cancelled and the patient will be considered a screen failure. The Sponsor should be notified of screen failures as soon as possible.

Sites will be notified by the Sponsor's Medical Monitor that enrollment to a cohort has been suspended so no further patients are recruited, until it is determined that either additional patients will be enrolled at the existing dose level or that enrollment to the next cohort may commence.

11.2 BLINDING AND UNBLINDING

Idronoxil will be administered at escalating doses in an open-label fashion. Patients will be allocated to 1 of 2 cohorts. No randomization or stratification is required.

12 DATA COLLECTION AND MANAGEMENT

12.1 METHODS

The Principal Investigator must ensure there will be primary source documentation for all patient data collected as part of the study, and the data will not be recorded directly onto the CRFs without the availability of such primary documentation, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the patient's CRF is appropriate. 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 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.

12.1.1 Case Report Form

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

12.1.2 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 in accordance with National regulations.

12.2 DATA MANAGEMENT

12.2.1 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).

12.2.2 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

13 STATISTICAL SECTION

13.1 SAMPLE SIZE

This is a sighting study intended to determine the safety of idronoxil (as NOX66 suppository dosage formulation) in combination with carboplatin, and to provide guidance as to the dosage combination of the two drugs that will be taken into later studies. A minimum of 8 patients per combination is considered adequate.

13.2 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.

The primary objectives of this study are to determine

(a) the tolerability, adverse event profile and any dose limiting toxicities (DLTs) of idronoxil (as NOX66) in combination with carboplatin in patients with refractory solid tumors, and
(b) the ability of idronoxil (as NOX66) in combination with carboplatin to deliver a meaningful anti-cancer effect in refractory tumours considered unlikely to respond to carboplatin.

Secondary objectives are:

1) to characterize the pharmacokinetic profile of idronoxil administered rectally as NOX66, and
2) to determine any correlation between biomarkers of idronoxil biological activity and any clinical anti-tumor activity or toxicity observed in patients treated with NOX66.

These objectives are to be addressed in the context of an open-label, dose-escalation study; therefore, statistical hypothesis-testing will not be performed, and analyses will be primarily descriptive in nature.

All patients will be included in the safety evaluation. Data will be presented by dose cohort. Data from Study NOX66-001A will be used to guide dosing for future Phase II trials.

Populations for Analysis: There will be three study populations defined for this study.

The safety population will consist of all patients who received at least one dose of idronoxil. This population will be used in all safety summaries.

The efficacy population will consist of all patients with measurable or evaluable disease at baseline who complete at least 1 cycle of treatment and undergo at least one follow-up tumor

evaluation.

The pharmacokinetic/biomarker population will be a subset of the safety and efficacy populations and consist of all patients who have sufficient idronoxil plasma data for analysis. All such patients will be evaluated unless significant protocol deviations have impacted the data. Changes to the procedures, which may impact the quality of pharmacokinetic data, will be considered significant protocol deviations. Examples include sample processing errors that lead to inaccurate bio- analytical results and/or inaccurate dosing on the day of pharmacokinetic sampling.

General Methodology: In general, data will be summarized by using counts and percents for discrete parameters, and by descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum) for continuous parameters. Subject disposition and baseline characteristics will be presented by dose cohort for all treated patients. Data will be analysed as collected. No imputation of missing data is planned. All collected data will be presented in the data listings by dose cohort.

Baseline Comparisons and Patient Disposition: Demographic and baseline disease characteristic data summarization will be performed in order to descriptively assess the comparability of dose cohorts. Data to be tabulated will include demographic features such as gender, age, and race, as well as disease specific status and medical history. The number and percentage of patients who complete the study or who withdraw for any reason will be presented by dose cohort.

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, ECG findings, 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 ECG findings and physical examinations, will be summarized throughout the study by visit for each dose level for all treated patients.

ECG parameters at each time point will be presented by patient and by time point. The results will be presented by dose cohort.

Efficacy Analysis: Tumor measurements will be assessed by radiologic methods at baseline and at subsequent intervals at the discretion of the Investigator but not greater than every 12 weeks. Efficacy variables will include overall response, duration of objective response, time to progression, progression free survival (PFS), and overall survival. Response and progression will be assessed according to RECIST (Eisenhauer et al., 2009).

Continuous data will be summarized by descriptive statistics, including sample size, mean, standard deviation, median and range. Categorical data will be summarized by the number and percentage of patients. For the time-to-event endpoints, Kaplan-Meier estimates will be plotted.

Median event time and the associated 95% confidence interval will be provided. In addition, all the data will be presented in the data listings. The final statistical analysis for the study will be scheduled when all patients have completed at least one course of study drug administration, have reached a study endpoint (e.g., DLT or disease progression), and have at least 28 days of follow- up.

Best overall response, duration of objective response (complete response or partial response), PFS, time to progression and overall survival will be listed for all patients with measurable or evaluable disease by dose level. Any patient with insufficient data to determine response will be classified as a non-responder. Among patients with an objective response, duration of objective response will be defined as the time from the initial CR or PR to the time of disease progression or death on study, whichever occurs first. For patients who are alive and have not experienced disease progression on study, duration of objective response will be censored at the day of the last tumor assessment. Time to disease progression is defined as the time from the first day of study drug administration (Day 1) to disease recurrence or progression on study. Progression free survival (PFS) is defined as the time from the first day of study drug administration (Day 1) to disease recurrence or progression, or death on study. Patients who are alive and disease progression-free will be censored at the date of last disease evaluation.

Pharmacokinetics: Plasma and 24-hour urine levels of idronoxil and idronoxil metabolites (idronoxil glucuronide, idronoxil sulphate) will be measured. Pharmacokinetic parameters will minimally include C_{max}, T_{max}, $AUC_{0\text{-}24h}$r, $AUC_{0\text{-}\infty}$, and $t_{1/2}$ and be calculated using standard analysis. Descriptive results will be presented for the pharmacokinetic parameters by dose cohort.

In the event that PK concentrations are not detectable at the time points necessary and a meaningful PK curve (i.e. concentration vs time) cannot be estimated, descriptive statistics will be used to summarize PK concentration.

Concomitant medications: Concomitant medications will be listed by dose cohort for all patients.

13.3 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.

13.4 INTERIM AND ADDITIONAL ANALYSIS

None.

14 MONITORING

14.1 MONITORING OF CASE REPORT FORMS

The study will be monitored by 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.

14.2 SAFETY DATA MONITORING

The Medical Monitor will review and evaluate all toxicities causally associated with idronoxil (NOX66). Once the fourth patient of Cohort 1 has completed 1 Cycle or when appropriate, depending on the DLTs experienced, a determination will be made that enrolment to this cohort continue. Once the eighth patient in Cohort 1 has completed 1 treatment cycle or when appropriate, depending on the DLTs experienced, the next dose level may commence.

14.3 AUDITING

Regulatory authorities, the HREC (Human Research Ethics Committee) equivalent 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 for quality assurance. The Investigator is obliged to facilitate this process by allowing full access.

15 ADVERSE EVENT REPORTING

Adverse events (AE) 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 (Table 12) and outcome categories should be defined (Table 13).

15.1 DEFINITIONS

15.1.1 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.

15.1.2 SAE

The definitions of SAEs are given below. The PI is responsible for ensuring that all staff involved in the trial are familiar with the content of this section.

An SAE or reaction 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 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 12.

15.1.3 Guidelines for Determining Causality and Severity

The criteria used for determining the relationship between the study drug/s and the Adverse Event are shown below:

Table 12. Adverse Event Relatedness Criteria to Study Drug

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 13: Adverse Event Outcome Category

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.

15.2 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 treatment, 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).

Deaths and other SAEs occurring > 30 calendar days after last study treatment 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 study trial treatment 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 using the contact information below.

Primary Contact Medical Monitor: Prof. Paul de Sousa	Telephone #: +61 2 9350 3910 Mobile #: +61 404 003 220 Email#: P.DeSouza@westernsydney.edu.au
Alternate Contact Study Manager: Marinella Messina	Telephone #: +61 2 9144 2223; Fax #: +61 2 9199 9600 Mobile #: +61 499 005 049 Email: marinella.messina@noxopharm.com

Pharmcovigilance (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.

15.2.1 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.

15.2.2 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.

15.2.3 Sponsor SAE Reporting Requirements

The Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonization (ICH) guidelines, NHMRC 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 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.

15.2.4 Pregnancy

If a study patient or a patient partner becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and faxed to the Sponsor expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sponsor.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. The previous completed Pregnancy Form must be updated to reflect the outcome of the pregnancy.

16 CONDUCT OF STUDY

16.1 HUMAN RESEARCH

The Protocol and all other relevant study documents (informed consent etc) will be submitted to the local HREC peer site and then to the Georgian Ministry of Health for approval. 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.

16.2 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). Compliance with these guidelines ensures compliance with the currently approved version of the Declaration of Helsinki latest version (October 2013) and any local legal and regulatory requirements.

16.3 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.

Notify the Human Research Ethics Committee (HREC) of all changes in the protocol, and provide documented approval of 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.

16.3.1 Protocol Violation and Reporting

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 the procedure described in Section 14.2.

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.

16.4 PROTOCOL AMENDMENTS

With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted. Notify the Human Research Ethics Committee (HREC) of all changes in the protocol, and provide documented approval of 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.

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.

17 PATIENT INFORMED CONSENT

The proposed informed consent form contains the 20 elements required for the provision of informed consent as described in ICH E6 (R2) 4.8. and the Declaration of Helsinki. Additionally, the informed consent form has been reviewed and approved by the Sponsor, the HREC and as applicable by national regulatory authority 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.

18 DISCLOSURE OF DATA

18.1 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 national health authorities, the Sponsor or delegate, 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 national 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 enrollment into the study that the patient's Protected Health Information (PHI) obtained during the study may be shared with the study, Sponsor, state and national authorities, and HREC regulatory inspections(s).

18.1.1 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 national regulatory authorities/agencies.
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 enrolment log (patient numbers and the corresponding patient names) to enable the records to be identified.

18.1.2 Prior to Study Commencement

Prior to the start of this study, all pre-investigational requirements must be met by the Principal Investigator and study site. These may include:

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 national authority acknowledging and or approving 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.

18.1.3 Document Retention

The Principal Investigator will retain copies of the following documents in a secure place for a period of at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years after the formal discontinuation of the clinical development of the investigational product. These documents may be retained for a longer period by agreement with the Sponsor.

These files must be made available for inspection upon reasonable request by authorised representatives of the Sponsor and the corresponding regulatory agencies for the purposes of regulatory approval.

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.

18.1.4 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.

18.1.5 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.

19 ADDITIONAL PATIENT CARE DURING POST-STUDY

19.1 EMERGENCY CONTACT

19.1.1 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.

19.1.2 Sponsor

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

19.2 Liability and Insurance

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

20 APPENDICIES

20.1 APPENDIX A

20.1.1 ECOG Performance Status*

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

* As published in Am. J. Clin. Oncol.: 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 B

20.2.1 Procedure for Collection of Plasma Samples

The patient does not have to fast prior to the taking of the PK samples.

Plasma samples will be analysed by the Sponsor for levels of idronoxil and biomarkers.

Draw blood from participant into a 5 mL K3 EDTA anti-coagulation blood collection tube provided in the sampling kit. Ensure adequate mixing between blood and EDTA by inverting tube back and forth for 30 seconds. Place tube on ice if the sample is not for immediate centrifugation. Samples must be centrifuged within 30 minutes of collection.

- Label a 5 mL K3 EDTA tube and plasma collection tube with participant study number, initials, sample date and time of draw.
- Centrifuge at 3000 rpm for 10 min (under refrigeration) within 30 minutes of blood collection.
- Carefully separate plasma for transfer into two 2 mL screw top tubes that have been labelled with the participant study number, initials, sample date and time of draw.

- Place each of the tubes in two separate fiber board freezer boxes noting the position number of the well in the box and freeze immediately at – 20°C or 80°C.
- Complete 2 separate inventory logs recording the specific sample position in each of the boxes on the corresponding inventory log line number.
- One box of frozen samples should be batched and shipped monthly. Call the Study Manager to arrange a courier for transfer of specimens. The remaining box of frozen samples is to be retained at the study site until shipment is requested.

20.2.2 Procedure for Collection of Urine Samples

Patients to be provided with *Instructions for the Collection of 24-Hour Urine Samples*.

- Urine to be returned to hospital within 24 hours of collection.
- Measure and record total volume.
- Dispense approximately 5 aliquots into 2 screw-top tubes provided that have been labelled with participant subject number, initials and sample date.
- Place each of the tubes in two separate fiber board freezer boxes noting the position number of the well in the box and freeze immediately at – 20°C or 80°C.
- Complete 2 separate inventory logs recording the specific sample position in each of the boxes on the corresponding inventory log line number.
- One box of frozen samples should be batched and shipped monthly. Call the Study Manager to arrange a courier for transfer of specimens. The remaining box of frozen samples is to be retained at the study site until shipment is requested.

20.3 APPENDIX C

20.3.1 References

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