CLINICAL STUDY PROTOCOL

Title: **A dose escalation and dose expansion study of NOX66 plus doxorubicin in anthracycline-naïve, adult patients with soft tissue sarcoma - CEP-2**

Protocol Number: **NOX66-004**

Product: **Idronoxil suppository (NOX66)**

Sponsor: **Noxopharm Limited**

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Version: **4.0**

Date: **21 March 2022**

SIGNATURES

SPONSOR

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

Dr Gisela Mautner

Chief Medical Officer, Noxopharm Limited

Date

INVESTIGATOR

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

[Name]

Principal Investigator

Date

1 PROTOCOL SYNOPSIS

Name of Company Sponsor	Noxopharm Limited Suite 3, 828 Pacific Highway, Gordon, NSW 2072 ('Noxopharm'), and incorporating its various subsidiary companies. (ABN 50 608 966 123)
Title of Study	A dose escalation and dose expansion study of NOX66 plus doxorubicin in anthracycline-naïve, adult patients with soft tissue sarcoma – CEP-2
Study Number	NOX66-004
IND Number	TBD
Study Identifier and Registry	ClinicalTrials.gov Identifier: NCT05100628
Development Phase	Phase I
Name of Active Ingredient	Idronoxil
Description of Investigational Product	Idronoxil (NOX66) is a multiple signal transduction regulator which results in cell death via extrinsic and intrinsic apoptosis, anti-angiogenesis, and immunomodulation via stimulation of natural killer cell activity. The study drug is formulated in a single use suppository with a proprietary lipophilic base containing 400 or 600 mg of idronoxil.
Indication	Anthracycline naïve adult patients with metastatic soft tissue sarcoma for whom treatment with doxorubicin is considered to be appropriate.
Study Objectives	**Primary objectives:** • To estimate the maximum tolerated dose (MTD) of NOX66 in combination with doxorubicin • To characterize the safety and tolerability of NOX66 alone and in combination with doxorubicin. **Secondary objectives:** • To determine single and multiple dose pharmacokinetics (PK) of idronoxil • To determine the preliminary efficacy and quality of life (QOL) of the MTD of NOX66 in combination with doxorubicin. **Exploratory objectives:** • To investigate the relationship between response to NOX66 plus doxorubicin and the following: a. Dose of NOX66 b. Histopathology (if prior tissue samples/slides are available) c. Genetic mutations d. Change in lipid profile from baseline e. Cytokine/chemokine and Ecto-NOX disulfide-thiol exchanger 2 (ENOX2) dynamics f. Acceptability of NOX66 dosage form

Study Design:	This is a Phase I, open-label, study of NOX66, given rectally in cohorts of patients with metastatic soft tissue sarcoma who have not been exposed to anthracycline therapy, using a fixed dose-escalation schema every 21 days to establish the MTD. In previous clinical trials, NOX66 has been administered to 18 cancer patients from 400 to 800 mg daily for 14 days prior to combination with carboplatin. In another study 25 patients received up to 16 days of 400 to 1200 mg/day while undergoing radiotherapy. Overall, NOX66 has been well tolerated. Dose-Escalation For all dose escalation cohorts, there will be 7 days of monotherapy treatment with NOX66 followed by a 5- day washout period prior to the start of combination cycles of NOX66 and doxorubicin. The purpose of the monotherapy treatment is to evaluate the safety and tolerability of NOX66 when administered alone and as well as single and multiple dose PK of idronoxil. The study will include three planned Treatment Groups (800, 1200, and 1800 mg daily) of 3 patients each. The first 3 patients will be entered at Dose Level 1 and will be given NOX66 (800 mg daily dose for 7 days) which will be followed by a washout period of 5 days. On Day 1 patients will be monitored for cardiac effects with 12-lead electrocardiograms (ECG) over 8 hours and PK samples will be collected for 24 hours. Patients will be closely monitored for any AEs during monotherapy. If no significant toxicities (defined below) are observed after 7 days of monotherapy and following a 5-day rest period, patients will enter combination therapy. This will commence with Cycle 1, which will consist of 7 days of NOX66 at 800 mg/day and on Day 2 of the 21-day cycle, doxorubicin will be administered at approximately 1 hour after application of NOX66. After a rest period of 2 weeks, Cycle 2 will be initiated with another 7 days of NOX66 treatment at the same dose (800 mg/day) and another dose of doxorubicin on Day 2. Patients will continue to be treated for up to 6 x 21-day cycles of NOX66 and doxorubicin in the same manner. Three new patients will be entered at the next dose level of NOX66, if no dose-limiting toxicities (DLTs) have occurred at the end of Cycle 1. In all cohorts, doxorubicin will be given initially at 75 mg/m^2 as an intravenous infusion over 15 minutes (or as per standard of care). This dose may be reduced to 60 mg/m^2, at the Investigator's discretion for unacceptable Grade $\geq$2 toxicity. Lower doses of doxorubicin (50% or 75% reduction) will be used of If serum bilirubin is 1.2 -3.0 mg/dL or 3.1 – 5.0 mg/dL prior to a cycle, respectively. Assessment of MTD At any given dose level, if 1 of 3 patients develops a DLT during Cycle 1, then dose escalation will halt temporarily, and an additional 3 patients will be enrolled at the same dose level. If no further DLTs occur, then dose escalation will resume. If 2 or more patients at a given dose level experience DLTs during Cycle 1, dose escalation will be halted, and that level will be declared the DLT dose

level. The previous dose level will then be considered for expansion to 6 patients in order to confirm that it is the MTD level. The MTD is defined as the dose level at which no more than 1 patient out of 6 experienced a DLT up to the end of Cycle 1. If in the first group at 800 mg daily (Cohort 1), 2 or 3 patients develop DLTs, then that dose level is considered to be the DLT level and 3 additional patients need not be tested at that level, but lower doses should be studied.

If no DLT is observed at 1800 mg (Cohort 3), dose escalation will be stopped. The proposed highest dose level (1800 mg) will be declared the MTD, and additional patients will be enrolled, if necessary, to ensure that a total of 6 patients are evaluated at this dose level.

The dose escalation scheme is presented in the following table.

Proposed Starting Dose and Dose Escalation Scheme for NOX66

Cohort	1	2	3
Increment	NA	50%	50%
Total daily dose (mg)	800	1200	1800
Daily regimen (mg)	400 BID	600 BID	600 TID

BID = twice daily, TID = three times daily. For each cohort, safety/tolerability and PK data will be collected on Days 1-2 and 7-8 for respective doses.

Assessment of toxicities and decisions about dose escalation and cohort expansion will be made by a Safety Review Committee, that will include at least one Sponsor representative participating investigators, and may also include a cardiologist or other outside consultants at the Sponsor's discretion.

<u>Assessment of DLTs</u>

Patients who withdraw in Cycle 1 for reasons other than safety or toxicity will be replaced. During the 7-day Monotherapy Period, any patient who develops a significant toxicity, as noted below, will be replaced.

For determination of DLT during Cycle 1, toxicity will be graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. Any of the following, if judged to be associated with NOX66 alone or in combination with doxorubicin (i.e., possibly-, probably-, or definitely related to), will be considered a DLT:

1) Grade 3 non-hematological toxicities (excluding alopecia) with the following exceptions:
   i. Grade 3 nausea/vomiting or diarrhea <72 hours with adequate antiemetic and other supportive care
   ii. Grade 3 fatigue <1 week
   iii. Grade 3 electrolyte abnormality that lasts 24 to 72 hours (Investigator's discretion for timeframe), is not clinically complicated

and resolves spontaneously or responds to conventional medical interventions.

2) Grade 4 non-hematologic (non-laboratory) toxicity of any duration
3) Grade 3 or Grade 4 febrile neutropenia of any duration not caused by doxorubicin. *It is well known that a dose-dependent, reversible leukopenia and/or neutropenia are the predominant manifestations of doxorubicin hematologic toxicity and are the most common acute dose-limiting toxicities of this drug. With the recommended dose schedule, leukopenia is usually transient, reaching its nadir 10 to 14 days after treatment with recovery usually occurring by the 21st day.*
4) Grade 3 thrombocytopenia in combination with a Grade 3 or greater blood and lymphatic system disorder, not attributable to doxorubicin
5) Grade 3 AST or ALT that is associated with a Grade 2 or greater rise in bilirubin

Growth factor support can be administered during combination cycles, except during Cycle 1 in the Dose Escalation Cohorts. The recommended Phase 2 dose (RP2D) may be defined as the highest dose administered at which no more than 1 patient (out of 6) experiences a DLT and the dosage form, including the dosing frequency, is acceptable to patients.

<u>Cohort Expansion</u>

After the Dose Escalation Part is completed, 16 patients will be enrolled into a Dose Expansion Cohort at the MTD of the combination of NOX66 and doxorubicin. All patients will enter directly into 21-day combination cycles and will be given NOX66 therapy for 7 days and doxorubicin will be administered on Day 2 (1 hour after the morning dose of NOX66 dose is administered). This will be followed by a 2-week rest period. Treatments will continue up to 6 cycles.

Treatment will be terminated upon disease progression, unacceptable toxicity or a maximum of 6 cycles. In patients who develop Grade 3 or 4 toxicity determined to be related to NOX66, the Investigator may reduce the dose or frequency of dosing by one level so that the patients can remain in the study. All patients will be actively followed up for about 14 months following completion of Cycle 6 (including scheduled visits every 3 months) followed by telephone follow-up / chart review, for progression free survival (PFS) and overall survival (OS), at 15 and 18 months following completion of Cycle 6.

<u>Pharmacokinetics</u>

During the Monotherapy phase, on Day 1 blood samples will be collected for PK analysis of idronoxil at pre-dose (within 15 minutes prior to dosing) and at 1, 2, 3, 4, 6, and 8 hours post application. On Day 2, a pre-dose sample will be collected prior to application of NOX66. This sample can be collected in the clinic or at the patient's home. Exact times for dosing and blood sampling will be recorded. If a bowel movement occurs, during the collection period, the time of each bowel movement should be recorded, and the collections should continue as planned. Blood plasma will be analysed for the quantification of

	idronoxil and metabolites using a validated liquid chromatography-tandem mass spectrometry method. On Day 7 of the NOX66 monotherapy period blood samples will be collected in the clinic for PK analysis of idronoxil at pre-dose (within 15 minutes prior to dosing) and at 1, 2, 3, 4, 6, and 8 hours post application after the morning dose. The remainder of the daily dose will be administered at 8 (TID regimen) or 12 (BID regimen) hours after the first morning dose of NOX66. On Day 8, the last PK sample will be obtained at 8 or 12 hours after the last dose of monotherapy on Day 7. The samples obtained on the first day of the washout period (Day 8) can be collected in the clinic or at the patient's home. The exact time the samples are collected must be recorded. Cycle 1: On Day 2, PK samples are to be collected prior to and at 1 and 2 hours post NOX66 administration and assayed for idronoxil and metabolites. PK samples are to be collected at 0.5, 4, and 6 hours after the end of the doxorubicin infusion and assayed for doxorubicin and doxorubicinol. On Day 7, PK samples will be obtained just prior to the morning dose of NOX66 and on Day 8 at 8 or 12 hours after the last dose on Day 7 for the TID and BID regimens, respectively. The exact times of dosing and collection of the blood samples for PK analysis after administration of NOX66 and doxorubicin must be recorded. Cycles 2, 4 and 6: On Day 2 PK samples are to be collected prior to administration of NOX66 and assayed for idronoxil and metabolites. On Day 2, PK samples are to be collected at 0.5 and 4 hours post doxorubicin infusion (note: 0.5-hour post-dose doxorubicin PK sample is not applicable at Cycle 4). The 0.5-hour sample will be assayed for doxorubicin and doxorubicinol and the 4-hour sample will be assayed for idronoxil and metabolites, doxorubicin, and doxorubicinol. Cycles 3 and 5: On Day 2, PK samples are to be collected 4 hours after the morning dose of NOX66 and just prior to the morning dose on Day 7 and on Day 8 at 8 or 12 hours after the last dose on Day 7 for TID and BID regimens, respectively. In the Dose Expansion Cohort, PK samples are to be obtained on Day 2 of Cycle 1 prior to morning dose of NOX66 and prior to the last morning dose of NOX66 on Day 7. PK samples for doxorubicin are to be collected at 0.5, 4 and 6 hours after the end of doxorubicin infusion. The 0.5-hour sample will be assayed for doxorubicin and doxorubicinol and the 4- and 6-hour samples will be assayed for idronoxil and metabolites, doxorubicin and doxorubicinol. On Day 2 of Cycles 2, 4 and 6, PK samples for doxorubicin are to be collected at 0.5 and 4 hours after the end of doxorubicin infusion and PK samples are to be collected prior to and at 4 hours post NOX66 and assayed for idronoxil and metabolites. On Day 2 of Cycles 3 and 5, PK samples are to be collected at 4 hours after the morning dose of NOX66 and just prior to the morning dose on Day 7 and assayed for idronoxil and metabolites.

	<u>Cardiac Monitoring</u> Day 1 Monotherapy: Triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.75, -0.5 and -0.25 hours prior to administration of NOX66 and at 1, 2, 5, and 8 hours after the first dose of NOX66 monotherapy. Additional ECGs in triplicate may be taken more frequently if QTc intervals exceed 500 ms during the study. The ECG parameters, QT, QT interval adjusted for the patient's heart rate by Fridericia's method (QTcF), PR, QRS, and RR intervals; heart rate; and T-wave amplitude, as well as any change from baseline, will be assessed and the relationship between NOX66 blood concentrations may be explored to determine if there is an effect on QTcF. Day 7 Monotherapy: Triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.75, -0.5 and -0.25 hours prior to administration of NOX66 and at 1, 2, 5, and 8 hours after the morning dose of NOX66. Holter monitoring will be used to record cardiac activity from 8 to 24 hours after the last morning dose of NOX66 monotherapy in each cohort. Cycle 1 Day 2: Triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.75, -0.5 and -0.25 hours prior to administration of NOX66 and at 1, 2, 5, and 8 hours after the morning dose of NOX66. Cardiac activity will be recorded with Holter monitoring from 8 to 24 hours after administration of NOX66. Cycles 2 to 6 Day 2 (combination of NOX66 and doxorubicin): Triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at - 0.25 hours prior to and at 1, 2, 5, and 8 hours post application of NOX66. Months 6, 9 and 12: Triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position. Echocardiography will be conducted at Screening, Day 1 of Cycles 3 and 5, and at the end of Cycle 6 or Early Termination (if the patient discontinues prior to 6 cycles). <u>Radiological Imaging</u> Tumor imaging (CT/MRI) for determination of response rate and PFS during the study, will be performed at Screening (if scans are not done within 28 days of registration and Cycle 1 Day 1), prior to the start of Cycles 1 (only in the Dose Escalation Cohorts if the baseline scan was done more than 28 days from C1D1), at the end of Cycles 2, 4 and 6, at 6, 9 and 12 months after the start of the combination therapy and at the End of Study or at Early Termination (ET) if the patient discontinues from the trial. <u>Safety Assessments</u> Adverse events (AEs) will be monitored by the Investigator during the study. Other safety assessments will include physical examination, vital signs, 12- lead ECGs (including Holter recordings), hematology, clinical chemistry, and urinalysis laboratory tests, as well as brain type natriuretic peptide (BNP) and troponin I assessments.

Study Period and Duration of Treatment	Screening will take up to 28 days prior to the first dose of NOX66. The study duration from initial administration of NOX66 to the last follow up is approximately 20 months including Screening. The lead-in NOX66 monotherapy period is 12 days, then 6 x 21-day cycles of NOX66 + doxorubicin, followed by 14 months of active follow up (including scheduled visits and telephone follow-up / chart review for PFS and OS).
Study Sites and Location	Approximately 12 sites in the United States and Australia
Patient Eligibility Criteria:	**Inclusion Criteria** Patients must satisfy all of the following criteria to be included in the study: 1. Adult patients (≥18years of age, inclusive at the time of signing the informed consent) with histologically confirmed diagnosis of metastatic or recurrent soft tissue sarcoma. 2. Patients for whom treatment with doxorubicin is considered to be appropriate (haemoglobin >10 g/dL, ANC >1000/μL^3, and platelets > 100,000/μL^3), serum bilirubin < 1x the institutional upper limit of normal (ULN) (unless known Gilbert's disease), AST or ALT < 3x institutional ULN, and creatinine clearance ≥50 mL/min as assessed by the Cockcroft-Gault equation. 3. Left ventricular ejection fraction ≥50%. 4. Disease that is considered measurable according to RECIST v1.1. 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. 6. Anticipated life-expectancy of at least 6 months. 7. For females of reproductive potential the following are considered highly effective acceptable forms of contraception: surgical sterilization (tubal ligation); total abstinence from sexual intercourse with the opposite sex; established hormonal birth control (e.g., oral, transdermal, injection, or implant) plus a barrier method or a double barrier method (intrauterine device, spermicide, or diaphragm plus condom) for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional month after the last dose of NOX66 or 6 months after the last dose of doxorubicin, whichever is longer. 8. For males of reproductive potential: vasectomy or use of highly effective contraception (e.g., condoms, abstinence) during the study and until 3 or 6 months after the last dose of NOX66 or doxorubicin, respectively, whichever is longer. **Exclusion Criteria** Patients who meet any of the following criteria will be disqualified from entering the study: 1. Histologically or cytologically confirmed Kaposi's sarcoma, gastrointestinal stromal tumor (GIST), extra-skeletal myxoid chondrosarcoma, epithelioid hemangioendothelioma, and desmoid tumor.

	2. Hepatic impairment defined as serum bilirubin > 1 x ULN (unless known Gilbert's disease) or either AST or ALT > 3x institutional upper limit of normal. 3. Unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months before study entry. 4. Untreated metastases to the CNS. 5. Received previous treatment with anthracyclines and anthracenediones. 6. Previous radiation therapy to the mediastinal or pericardial area. 7. A known allergy to any of the treatment components. 8. Active or chronic infection with human immunodeficiency virus (HIV). NOTE: Patients with chronic HIV infection, on ongoing treatment with anti-viral medications, who have an undetectable viral load are not considered to be infectious and can be included in this study. 9. Pregnant (positive urine pregnancy test) or lactating. 10. Patient not willing to use suppositories. 11. Patients with a colostomy. 12. Patients who have had a colectomy (total or left hemicolectomy) with re-anastomosis. 13. Patients for whom administration of the suppositories are likely to cause pain (e.g., inflamed hemorrhoids, fissures, or lesions of the anus or rectum). 14. Patients with fecal impaction, chronic idiopathic constipation, or chronic diarrhea or alternating irritable bowel disease. 15. Patients with inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis). 16. Previous treatment with an investigational agent or the non-approved use of a drug or device within 4 weeks before study entry 17. Uncontrolled diabetes mellitus. 18. Patients who require concomitant use of strong inhibitors or inducers of CYP3A4, CYP2D6 or P-glycoprotein (P-gp).
Dosage Form, Dose, and Route of Administration:	Idronoxil will be provided in 400 mg and 600 mg strength suppositories, for BID or TID rectal administration by trial participants. Doxorubicin provided as 10 mg, 20 mg, 50 mg or 200 mg powder for injection to be administered as an intravenous infusion, over 15 minutes (or as per standard of care), every 21 days at the recommended dose of 75 mg/m^2. In addition, the Investigator may use dexrazoxane to reduce the incidence and severity of cardiomyopathy associated with the use of doxorubicin. However, the degree of myelosuppression may be increased at Cycles 5 and 6 with the use of dexrazoxane. Doxorubicin should be given within 15 minutes after beginning the infusion with dexrazoxane. [Note: For breast cancer patients, dexrazoxane is recommended when doxorubicin cumulative dosage is ≥ 300 mg/m^2].
Criteria for Evaluation	The following criteria will be used to evaluate the safety of NOX66 alone and in combination with doxorubicin: • 24-hour Holter/ monitoring • 12-lead ECGs (in-patient) • Serum transaminases, bilirubin • BNP and troponin I • Echocardiography

	• Complete blood count • Electrolytes (Ca^{++}, Mg^{++}), PO_4, BUN, creatinine The following criteria will be used to evaluate the efficacy of NOX66 alone and in combination with doxorubicin: • RECIST v1.1: Disease Control Rate (DCR) defined as [(stable disease (SD)+ partial response (PR) + complete response (CR)/All)], overall response rate (ORR) • Overall survival (OS), Progression Free Survival (PFS) • European Organization for Research and Treatment of Cancer: Core Quality of Life Questionnaire v3.0 (EORTC QLQ-C30) • Fatigue Severity Scale (European Organisation for Research and Treatment of Cancer: Cancer Related Fatigue Module - EORTC QLQ-FA12) • Brief Pain Inventory (short form) • Suppository Acceptance Questionnaire The following criteria will be used to evaluate the PK of idronoxil and metabolites in blood plasma after single and repeated doses of NOX66: • Maximum concentration (C_{max}) • Time to reach maximum concentration (T_{max}) • Trough concentrations after repeated administration • Area under the concentration-time curve up to last measurable time point and infinity (AUC_{last} and AUC_{inf}) • Area under the concentration-time curve over a dosing interval after repeated administration (AUCτ) • Terminal elimination half-life (if possible) Pharmacokinetic parameters of idronoxil and metabolites obtained on Day 7 will be compared to Day 1 values. Sparse PK sampling for determination of idronoxil and metabolites, doxorubicin and doxorubicinol concentrations will be obtained during the treatment cycles to assess variability of exposure of idronoxil and doxorubicin in an exploratory manner. The following biomarkers will be evaluated to assess the relationship between response to NOX66 and doxorubicin: • Genetic mutations • Change in lipid profile from baseline • Cytokine/chemokine and ENOX2 dynamics
Number of Patients (Planned)	Up to approximately 34 patients with metastatic soft tissue sarcoma will be studied if the MTD is determined with the maximum dose planned for this study. If a minimum number of patients is studied per dose escalation, the expected number of patients is approximately 28.
Statistical Methods	**Sample size:** Up to 18 patients may be enrolled in the Dose Escalation part of this study, in cohorts of 3 or 6 patients at each specified dose. Sixteen patients will be enrolled in the Cohort Expansion part of this study. Patients must take at least 80% of their prescribed doses to be considered eligible for MTD evaluation. These sample sizes will be adequate to provide a safety profile for dose selection and to describe the PK characteristics of idronoxil. If patients are

	replaced in the Monotherapy period, in Cycle 1 or 2, the number of patients will be higher than 34. **Analysis sets:** There will be two analysis sets • Safety Set: All patients treated with at least one dose of idronoxil will be included in the Safety Set (SS). All analyses of safety, toxicity, and PK will be performed for this set. • Full Analysis Set (FAS): All patients who completed at least one cycle of combination therapy (at any NOX66 dose). Analyses of efficacy, tolerability, and biomarkers will be performed for the FAS. Separate summaries may be provided for patients participating in the Dose Escalation and Dose Expansion parts. **Safety (Primary analysis):** The safety profile will be based on Serious Adverse Events (SAEs), Treatment Emergent Adverse Events (TEAEs), standard clinical laboratory parameters (clinical chemistry, hematology, urinalysis), vital signs measurements, ECG parameters, and physical examination findings. Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities and summarized by dose when NOX66 is given alone or in combination with doxorubicin. The number and percentage of patients reporting TEAEs will be calculated overall, by system organ class, and by preferred term for each dose level. Adverse events will also be graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0. Serious Adverse Events (SAEs) will be summarized separately. Cardiac AEs (including clinically significant abnormalities in ECG rhythm and waveform morphology reported as TEAEs) and changes in echocardiographic parameters will be summarized. Descriptive statistics will be provided for demographics, baseline characteristics, and exposure to treatment by cohort. Univariate summary statistics will be provided by dose group at each visit for quantitative laboratory parameters and vital signs and for the change from baseline in these parameters. For laboratory values and vital signs with defined CTC grades, shift tables will be provided for CTC grades from baseline to end of study and from baseline to worst value on study. Univariate summary statistics will be presented for ECG parameters for the value at each measurement time point and the change from baseline to each measurement time point. A similar analysis will be provided for the worst value of each ECG parameter on study. Findings from physical examinations and ECOG performance status will be summarized by dose of NOX66 given alone or in combination with doxorubicin. **Pharmacokinetics (Secondary analysis):** Individual blood concentration-time data and blood PK parameters will be summarized using descriptive statistics by dose and sampling time for idronoxil and metabolites. Separate summaries will be provided for PK

	samples collected for single-dose administration, repeated administration, and administration in combination with doxorubicin. Blood PK parameters will be determined by noncompartmental analysis for idronoxil and metabolites and will be summarized by dose and treatment day. Concentrations of idronoxil obtained in the presence of doxorubicin will be compared to monotherapy. Concentrations of doxorubicin and doxorubicinol will be determined after the administration of the infusion in the presence of NOX66 and will be compared to historical controls. The relationship between PK parameters and AEs and other safety findings may be assessed by graphical methods and special summary tables. **Efficacy (Secondary analysis):** The DCR, ORR, and the incidences of CR, PR, SD, and Progressive Disease (PD) as assessed by RECIST v1.1 criteria will be summarized for the MTD of the combination by counts and percentages and exact 95% confidence intervals at the end of Cycles 2, 4, and 6, at the 6-month, 9-month, and 12-month follow-up visits and at End of Study. Survival functions will be computed for OS and PFS by the Kaplan-Meier method. Estimates of median OS and median PFS will be presented. **Quality of Life (Secondary Analysis):** Quality of Life analyses will be performed for the FAS. Scale measures from the EORTC QLQ will be presented by dose for each visit, along with change from baseline to each visit. Brief pain inventory items and fatigue parameters will be summarized by dose at each visit as well as the change from baseline to each visit. **Exploratory Analysis:** An exploratory analysis will be performed to assess various factors which may contribute to response to the combination of NOX66 and doxorubicin. These factors include, NOX66 dose or exposure, cytokine, chemokine and ENOX2 response, lipidomic profiling (capturing over 300 lipid species as determined by liquid chromatography-tandem mass spectrometry), histopathology, and specific genetic mutations. The acceptability of the suppository dosage form by patients will also be determined. **Interim Analysis:** An interim analysis will be performed after all patients in the Dose Escalation part of the study have either discontinued or completed 3 treatment cycles, whichever comes first. A second interim analysis may also be performed after 50% of the patients in the expansion cohort have either discontinued or completed 3 treatment cycles. The results from these analyses will not be used to modify the design of this study or to stop it.

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ABBREVIATION	DEFINITION
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{inf}	Area under the concentration-time curve up to infinity
AUC_{last}	Area under the concentration-time curve up to the last measurable time point
AUCτ	Area under the concentration-time curve over a dosing interval
BID	Twice daily
BNP	Brain type natriuretic peptide
C_{max}	Maximum observed blood concentration
CRO	Contract research organization
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
DCR	Disease control rate
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ENOX2	Ecto-NOX disulfide-thiol exchanger 2
EORTC	European Organization for Research and Treatment of Cancer
ET	Early termination
GCP	Good Clinical Practice
HEENT	Head, ears, eyes, nose, throat
HR	Hazard ratio
HIV	Human immunodeficiency virus
IC_{50}	Inhibitory concentration of 50%
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

ABBREVIATION	DEFINITION
IRB	Institutional review board
Kel	Terminal elimination rate constant
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
ORR	Objective response rate
OS	Overall survival
P-gp	P glycoprotein
PFS	Progression free survival
PK	Pharmacokinetics
PD	Progressive disease
PR	Partial response
QD	Once daily
QOL	Quality of life
QRS	QRS interval on electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
RT	Radiotherapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAQ	Suppository Acceptance Questionnaire
SD	Stable disease
SRC	Safety review committee
STS	Soft tissue sarcomas
TEAE	Treatment-emergent adverse event
TID	Three times daily
T1/2	Terminal elimination phase half-life
T_{max}	Time to reach maximum concentration

5 ROLES AND RESPONSIBILITIES

5.1 SPONSOR

Noxopharm Limited (Noxopharm) is responsible for the study design, data collection and management, analysis and interpretation of data, writing of the Clinical Study Report (CSR), and publication of the study results. The study is funded by Noxopharm.

Noxopharm reserves the right to terminate the study at any time. A written explanation will be provided to the Investigator should the study be terminated. Each Investigator is responsible to inform the Institutional Review Board (IRB) of such a decision and to return all study materials to the Sponsor. The Sponsor will also update the status of the study in the Annual Report to FDA.

5.2 INVESTIGATOR AND SITES

The primary roles and responsibilities of all Investigators and other study personnel at all sites are to recruit the appropriate patients for this study, monitor the safety of all the patients and follow the protocol. This study will be conducted in the US and Australia and will take place in academic hospitals or treatment centers.

The sites and Investigators will be paid for their time and use of facilities. There are no conflicts of interest.

5.3 KEY NOXOPHARM PERSONNEL

Individuals and their roles from Noxopharm are shown below.

Function	Name	Affiliation
Chief Medical Officer	Dr Gisela Mautner	Noxopharm
Medical Monitor	Dr Marissa Lim	Noxopharm

5.4 OVERSIGHT COMMITTEE

The Safety Review Committee, (SRC) will include at least one sponsor representative, participating Investigators and may also include a cardiologist or other outside consultants at the Sponsor's discretion. The primary role of the SRC is to assess toxicities, if needed, to determine if they meet the definition of a dose-limiting toxicity (DLT) and make decisions about dose escalation and what dose will be used in the cohort expansion.

6 INTRODUCTION

6.1 BACKGROUND AND RATIONALE

Soft tissue sarcomas (STSs) are mesenchymal neoplasms that can arise from any site within the body, including the extremity, trunk, retroperitoneum, and head and neck. These are biologically heterogeneous diseases, with over 50 subtypes that vary by molecular, histological, and clinical characteristics. The most common subtypes of high-grade STS include

undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors. Collectively, STSs are rare, accounting for <1% of adult cancers, with an estimated 12,310 new cases in 2016 in the United States (1). Unfortunately, up to 50% of high-risk patients with high-grade STS develop metastases and die from their disease (2). Among the young adult and pediatric population under 20 years of age, STS is one of the top five causes of cancer-related death (1). The median overall survival (OS) for advanced, metastatic STS has historically been in the range of 12 months, while more recent randomized studies have noted survival approximating 18–19 months (3-10). Nonetheless, improvements in the management of high-grade STS are needed.

Anthracyclines (e.g. doxorubicin) remain the standard of care for first-line therapy in high- grade STS, regardless of subtype, presentation and patient characteristics. Anthracyclines intercalate into deoxyribonucleic acid (DNA), thereby blocking DNA and ribonucleic acid synthesis, while also interfering with topoisomerase II, leading to DNA breakage. Doxorubicin has single-agent activity in high grade STS, and demonstrates a dose–response relationship, with doses lower than 60 mg/m^2 associated with inferior efficacy (11, 12). Because of its toxicity profile however, most dose-intensive treatment schedules administer doxorubicin at 75 mg/m^2 for otherwise fit patients (13, 14).

In a large multicenter 455-patient study, doxorubicin (75 mg/m^2) in combination with an alkylating agent (e.g. ifosfamide), given alone every 3 weeks over 6 cycles showed a higher response rate (RR), 26.5% compared with doxorubicin alone 13.6% ($p < 0.0006$). The combination also significantly improved progression free survival (PFS) from 4.6 months to 7.4 months [hazard ratio (HR) 0.74, $p = 0.003$], but there was no significant difference between the two treatments in OS (14.3 months versus 12.8 months, HR 0.83, $p = 0.076$). Despite its efficacy, there was higher toxicity when using the combination, with 18% of patients receiving doxorubicin plus ifosfamide and 3% of patients receiving doxorubicin alone being unable to complete the planned 6 cycles of therapy due to adverse events (AEs). It should be noted the most common Grade 3–4 toxicities when administering doxorubicin and ifosfamide are related to bone marrow suppression which highlights the need for regular blood-count monitoring, supportive transfusions and growth factor support (14, 15, 16). These findings suggest that combination chemotherapy provides better outcomes for tumor shrinkage, but improvement in OS is lacking, although part of the problem may be overlapping toxicities in the regimens that have been studied.

In a combined Phase 1b/2 study (n=15/133), olaratumab, a platelet-derived growth factor receptor-α blocking antibody in combination with doxorubicin was evaluated for the treatment of anthracycline-naïve STS (17). Patients were treated for up to 8 cycles with the combination doxorubicin and olaratumab and longer with olaratumab alone. Although the median PFS was not significantly improved with olaratumab at 6.6 months compared with 4.1 months for doxorubicin alone, the median OS was 26.5 months with olaratumab, compared with 14.7 months in the doxorubicin alone arm. This almost 1-year difference in OS indicates

that another agent with a different mechanism of action and toxicity profile from doxorubicin may provide improved outcomes in STS, compared to doxorubicin alone.

Idronoxil, a small molecule, acts by binding Ecto-NOX disulfide-thiol exchanger 2 (ENOX2) – a tumor-specific form of external membrane NADH oxidase. As such, the activity of idronoxil is highly specific to tumor cells. Binding of idronoxil to ENOX2 leads to a disruption of the sphingomyelin pathway, preventing the conversion of ceramide to sphingomyelin- 1- phosphate (S1P), and subsequently a cascade of events leading to apoptosis. *In vitro* idronoxil potently sensitizes a broad range of cancer cell lines and adds to the cytotoxic effects of standard chemotherapeutic agents from various classes. In addition, it has been demonstrated that Idronoxil reverses pre-existing resistance (e.g. sensitizes platinum-resistant cells to carboplatin) (18, 19, 20).

In other studies, optimal sensitization with idronoxil occurred with a 24-hour period of idronoxil pre-treatment followed by a 120-hour treatment with a chemotoxin. Several clinical trials have been conducted with idronoxil using intravenous and oral routes of administration. The addition of oral idronoxil [(400 mg three times daily (TID)] to platin based therapy provided no clinical benefit in patients with platinum-resistant ovarian cancer, but there was some evidence of activity in small cell sarcoma or adenocarcinoma of the cervix, vagina or vulva. The high rate of metabolism of oral idronoxil may have led to the failure to show clinical activity in these studies.

To circumvent the high rate of metabolism, a rectal formulation was developed, and one Phase 1 study has been completed in 18 patients with solid tumors. Idronoxil suppository was administered [400 mg once daily (QD) or 400 mg twice daily (BID)] for 14 consecutive days followed by 7 days off treatment. After completion of the NOX66 monotherapy period, carboplatin was added on Day 2 of 7 consecutive days of NOX66 treatment in each cycle. The combination phase of the study consisted of 3 cycles of NOX66 and low-dose carboplatin (AUC=4) followed by three cycles of NOX66 and a higher dose of carboplatin (AUC=6). The patients who completed the monotherapy and all cycles, received NOX66 for a maximum of 56 days and carboplatin for up to 6 cycles. The most common treatment-emergent adverse event (TEAE) by System Organ Class was blood and lymphatic system disorders, with 44% of the patients, half of which experienced mild to severe anemia. In terms of tumor response, at Cycle 6, 1 patient had a partial response (PR), and most had stable disease (SD). Of the 3 deaths in the study, 2 were due to progressive disease and one may have been related to the combination of NOX66 and carboplatin, although an autopsy was not performed.

An ongoing Phase 1 study is evaluating the combination of NOX66 plus palliative doses of radiotherapy (RT) in patients with metastatic castrate resistant prostate cancer who have failed all available treatment. In the first part of the study (dose escalation), 14 patients were treated with either 400, 800 or 1200 mg/day NOX666 (n=4-6/dose) for up to 16 days. Radiotherapy was administered over 8 days and NOX66 treatment began on the day prior to RT and continued until 7 days following completion of RT. In the second part of the study a dose expansion cohort (n=12) with 1200 mg NOX66 is underway.

In 25 patients studied to date, mild (Grade 1) TEAEs of fatigue have been attributed to both NOX66 and radiation, while occurrences of mild dry mouth, oral mucositis, and stomatitis have been considered related to NOX66 alone. Cases of mild radiation dermatitis, oropharyngeal pain, and moderate anaemia and urinary tract infection have been considered related to RT alone.

Three patients in the 800 mg dose cohort died due to disease progression, ≥30 days after the last NOX66 dose. Two of these patients experienced severe (Grade 3) TEAEs. One patient developed lymphopenia, and hypocalcemia immediately after completion of treatment, followed one month later by nausea, vomiting, and subsequent death. The other patient developed anaemia after completion of treatment and hypophosphatemia 20 days post treatment completion both of which resolved. Almost three (2.75) months later the patient died. One patient in the 1200 mg dose cohort died due to disease progression ≥30 days after the last NOX66 dose. None of these deaths were considered related to NOX66.

The majority of all other TEAEs were mild to moderate (Grades 1-2). Other Grade 3 TEAEs were asthenia, back pain or bone pain, which were reported in 3 patients.

The present study will assess the safety, tolerability, and pharmacokinetics (PK) of NOX66 using a wider range of doses than were tested in the first Phase 1 studies as well a different cytotoxic agent. In addition, preliminary evaluation of the efficacy as well as safety/tolerability and PK for NOX66 will be made in combination with doxorubicin in patients with metastatic STS. Although doxorubicin is used as first line therapy in this disease, median survival is still only about 1 year and there is significant toxicity. Based on nonclinical data as noted in Section 6.2 the effectiveness of doxorubicin could be enhanced in the presence of NOX66.

Additional information on NOX66 may be found in the Investigator's Brochure.

6.2 CHOICE OF COMPARATOR OR CONTROL

The present study is designed to find the maximum tolerated dose (MTD) of the combination of NOX66 with doxorubicin in patients with STS, and therefore no control group or comparator is needed for this study.

All patients will be treated with doxorubicin which is widely held as the initial standard of care for metastatic STS. One week prior to initiation of doxorubicin, patients in the Dose-Escalation Cohorts will also receive 7 days of NOX66 monotherapy which has been shown to be cytotoxic to sarcoma cell lines (n=19) *in vitro* with IC_{50} values ranging from 0.3 to 18.4 µM (median 5.2 µM).

In the Dose Expansion Cohort, all patients will be treated for 1 day with NOX66 (at the MTD of the combination of NOX66 and doxorubicin), before receiving doxorubicin on Day 2 of a 21-day cycle. On Days 2 to 7, NOX66 will be given at the same dose as on Day 1. No therapy is administered from Days 8 to 21 of each treatment cycle.

All patients are eligible to receive up to 6 cycles of doxorubicin.

7 STUDY OBJECTIVES

7.1 PRIMARY OBJECTIVES

- To estimate the maximum tolerated dose (MTD) of NOX66 in combination with doxorubicin
- To characterize the safety and tolerability of NOX66 alone and in combination with doxorubicin.

7.2 SECONDARY OBJECTIVES

- To determine single-and multiple-dose pharmacokinetics (PK) of idronoxil
- To determine the preliminary efficacy and quality of life (QOL) of the MTD of NOX66 in combination with doxorubicin.

7.3 EXPLORATORY OBJECTIVES

- To investigate the relationship between response to NOX66 plus doxorubicin and the following:
    - Dose of NOX66
    - Histopathology (if prior tissue samples/slides are available)
    - Genetic mutations
    - Cytokine/chemokine and ENOX2 dynamics
    - Change in lipid profile from baseline Acceptability of NOX66 dosage form

8 STUDY DESIGN AND OVERALL INVESTIGATIONAL PLAN

8.1 OVERALL INVESTIGATIONAL PLAN

This is a Phase I, open label, dose escalation and dose expansion study of NOX66 given rectally, in cohorts of patients with metastatic STS who have not been exposed to anthracycline therapy, using a fixed dose escalation schema every 21 days to establish the MTD of the combination of NOX66 and doxorubicin.

8.1.1 DOSE-ESCALATION

For all dose escalation cohorts, there will be 7 days of monotherapy treatment with NOX66 followed by a 5- day washout period prior to the start of combination cycles of NOX66 and doxorubicin. The purpose of the monotherapy treatment is to evaluate the safety and tolerability of NOX66 when administered alone and as well as single and multiple dose PK of idronoxil.

The dose-escalation part of the study will include three planned Treatment Groups (800, 1200, 1800 mg daily) of 3 patients each. The first 3 patients will be entered at Dose Level 1 and will receive daily doses of NOX66 for 7 days. All of these doses, except for the 1800 mg have been evaluated in 2 previous clinical trials and have been relatively well tolerated as monotherapy for 14 days and in combination with carboplatin for 42 days.

After a rest period of 5 days and if no significant toxicities (DLT equivalent toxicity) have occurred, patients will enter the combination therapy part of the study which will consist of up to 6 x 21-day treatment cycles. Each cycle will consist of 7 days of NOX66 (at the assigned dose), doxorubicin (75 mg/m^2) on Day 2 of the 21-day cycle (administered at approximately 1 hour after rectal application of NOX66) and a rest period of 2 weeks.

For the 800 mg and 1200 mg dose levels NOX66 will be administered twice-daily (BID) with a 400 mg or 600 mg suppository, respectively, and the 1800 mg dose level will entail administration of a 600 mg suppository three times daily (TID). In all cohorts, doxorubicin will be given initially at 75 mg/m^2 as an intravenous infusion over 15 minutes (or as per standard of care). This dose may be reduced to 60 mg/m^2, at the Investigator's discretion for unacceptable Grade $\geq$2 toxicity. A dose reduction of 50% is recommended if serum bilirubin is 1.2 -3.0 mg/dL prior to a cycle. If serum bilirubin is 3.1-5.0 mg/dL prior to a cycle, a 75% dose reduction of doxorubicin is recommended.

The MTD of the combination of NOX66 and doxorubicin will be determined over the first 21-day interval (Cycle 1) following monotherapy with NOX66 and in combination of doxorubicin-in 1 of 3 consecutive dose cohorts. The MTD of the combination will either be considered one dose level of NOX66 lower than the dose which produces ≥ 2 DLTs in 3 or 6 patients, depending if a DLT occurred in the first 3 patients, or the highest dose level tested (1800 mg daily) if the aforementioned condition does not occur. A DLT will be defined as a protocol-specified adverse event of toxicity Grade 3-4 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] V 5.0) which is considered possibly, probably, or definitely related to the combination of NOX66 and doxorubicin (Section 8.3).

Since this is a multicenter trial, the sites are to notify the Sponsor or designee when a patient has been declared eligible to participate. After 3 patients have completed a 21-day treatment cycle of the combination of NOX66 and doxorubicin and all the safety data are available, assessment of toxicities and decisions about dose escalation and cohort expansion (see below) will be made by the SRC, which will include at least one Sponsor representative participating Investigators, and may also include a cardiologist or other external consultants at the Sponsor's discretion. Recommendations from the SRC could include 1) repeat a dose level, 2) await further safety data if follow-up is pending for patient(s) as determined by the Investigator(s), 3) discontinue the study, 4) escalate the dose to next possible level or 5) take other actions.

Three new patients will be entered at the next dose level of NOX66, if there were no DLTs or only 1 of 6 patients had a DLT at the end of the first cycle.

If no DLT is observed at 1800 mg (Cohort 3), dose escalation will be stopped. The proposed highest dose level (1800 mg) will be declared the MTD, and additional patients will be enrolled, if necessary, to ensure that a total of 6 patients are evaluated at this dose level.

8.1.2 COHORT EXPANSION

After the dose escalation part is completed, 16 patients will be enrolled into a Dose Expansion Cohort at the MTD of the combination. All patients will enter directly into 21-day combination cycles and will be given NOX66 therapy for 7 days and doxorubicin will be administered on Day 2. This will be followed by a 2-week rest period. Treatments will continue up to 6 cycles.

For both the Dose Escalation and Cohort Expansion groups, treatment will be terminated upon disease progression, unacceptable toxicity or a maximum of 6 cycles. In patients who develop Grade 3 or 4 toxicity determined to be related to NOX66, the Investigator may reduce the dose or frequency of dosing by one level so that the patients can remain in the study. Furthermore, all patients will be actively followed up for about 14 months after completion of Cycle 6 (including scheduled visits every 3 months) followed by telephone follow-up/chart review, for PFS and OS, at 15 and 18 months from the start of Cycle 1.

8.2 STUDY TREATMENTS

Idronoxil is a multiple-signal transduction regulator which results in cell death via extrinsic and intrinsic apoptosis, anti-angiogenesis, and immunomodulation via stimulation of natural killer cell activity. The study drug (NOX66) is formulated in a single use suppository with a proprietary lipophilic base containing 400 or 600 mg of idronoxil. The suppository will be self-administered by each patient according to the dose level assigned.

Doxorubicin is a cytotoxic anthracycline antibiotic that binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. Doxorubicin hydrochloride for Injection, USP, a sterile red-orange lyophilized powder for intravenous use only, is available in 10, 20 and 50 mg single dose vials and a 150 mg multidose vial. It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. Prior to the start of each cycle, patients must have a minimum ANC of 1000/μL^3 to reduce the risk of infection from suppository insertion.

8.3 DEFINITION AND DETERMINATION OF MTD AND DLT

8.3.1 DEFINITION OF MTD

The MTD is defined as the maximum dose level at which no more than 1 patient out of 6 experienced a DLT at the end of Cycle 1.

8.3.2 DETERMINATION OF MTD

If at any given dose level, when 1 of 3 patients develops a DLT during Cycle 1, then the dose escalation will halt temporarily, and an additional 3 patients will be recruited at the same dose level. If no further DLTs occur, then dose escalation will resume with the next 3 patients receiving the next higher dose of NOX66. If there are 2 or more patients (out of 6) who

experience DLTs during Cycle 1, dose escalation will be halted, and that level will be declared the DLT dose level. The previous dose level will then be considered for expansion to 6 patients in order to confirm that it is the MTD level. If in the first group at 800 mg, 2 or 3 patients develop DLTs then that dose level is considered to be the DLT level and 3 additional patients need not be tested at that level, but lower doses should be studied.

8.3.3 DEFINITION OF DLT

Any of the following, if judged to be associated with the combination of NOX66 and doxorubicin (i.e., possibly-, probably-, or definitely related), during Cycle 1, at each dose level, will be considered a DLT using the NCI-CTCAE Version 5.0:

1) Grade 3 non-hematological toxicities (excluding alopecia) with the following exceptions:

   i. Grade 3 nausea/vomiting or diarrhea <72 hours with adequate antiemetic and other supportive care

   ii. Grade 3 fatigue <1 week

   iii. Grade 3 electrolyte abnormality that lasts 24 to 72 hours (Investigator's discretion for timeframe), is not clinically complicated and resolves spontaneously or responds to conventional medical interventions.

2) Grade 4 non-hematologic (non-laboratory) toxicity of any duration
3) Grade 3 or Grade 4 febrile neutropenia of any duration not caused by doxorubicin*. It is well known that a dose-dependent, reversible leukopenia and/or neutropenia are the predominant manifestations of doxorubicin hematologic toxicity and are the most common acute dose-limiting toxicities of this drug. With the recommended dose schedule, leukopenia is usually transient, reaching its nadir 10 to 14 days after treatment with recovery usually occurring by the 21st day.*
4) Grade 3 thrombocytopenia in combination with a Grade 3 or greater blood and lymphatic system disorder, not attributable to doxorubicin
5) Grade 3 AST or ALT that is associated with a Grade 2 or greater rise in bilirubin

Based on the limited experience with NOX66 and the known toxicities of doxorubicin, it is possible that there may be overlapping toxicities in terms of anemia, neutropenia, nausea, and asthenia.

If patients develop any DLT during NOX66 monotherapy and/or during Cycles 2 to 6 of the combination, these will be considered "DLT equivalent toxicity" and will be recorded in the eCRF. Growth factor support (except during Cycle 1 in the Dose Escalation Cohorts) or other supportive medication (anti-emetics) at any cycle may be given at the discretion of the Investigator.

8.3.4 DETERMINATION OF DLT

At the end of Cycle 1, all patients in each cohort will be evaluated for DLTs for dose escalation of the next cohort. During the other cycles, assessment of DLTs will be done on an ongoing basis, and if they arise, the doses of NOX66 or doxorubicin or both may be reduced. If a new DLT is most likely related to doxorubicin, the dose of doxorubicin should be reduced to 60 mg/m^2 or to 37.5 or 18.75 mg.m^2 (based on serum bilirubin) or delayed until toxicity has been resolved or improved. If the DLT is likely related to NOX66, the Investigator may lower the NOX66 dose and/or extend the dosing interval.

8.3.5 EVALUABLE PATIENT

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

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

8.3.6 PATIENT REPLACEMENT

The following guidelines will be used to determine when a patient can be replaced

- During the Monotherapy period in the Dose Escalation part of the study, if a patient who is not tolerating the assigned dose of NOX66, may be replaced with another patient, following a joint decision between the Investigator and Medical Monitor. A maximum of 3 replacements is allowed in each dose level in the Monotherapy period.
- If any patient withdraws consent during Monotherapy period or during Cycle 1, he/she will be replaced with another patient.
- If any patient who has not taken at least 80% of the prescribed daily doses of NOX66 during Monotherapy period and Cycle 1, will be replaced with another patient.
- During the Dose Expansion Part, patients who have not completed at least 2 complete cycles of treatment, will be replaced with additional patients, until at least 12 patients have completed 2 cycles.

The recommended phase 2 dose (RP2D) may be defined as the highest dose of the combination administered if no DLTs are observed and the dosage form is acceptable to patients.

9 STUDY PARTICIPANTS

9.1 STUDY POPULATION

Up to approximately 34 patients with metastatic STS will be studied. Patients will be selected at cancer centers that have a sufficient number of sarcoma patients who would be willing to participate in clinical trials, and the center is equipped to provide rapid, comprehensive

treatment for different types of sarcoma. The Investigators chosen for this study must have expertise in the treatment of sarcoma as well as in the administration of doxorubicin.

9.2 INCLUSION CRITERIA

Patients must satisfy all of the following criteria to be included in the study:

1. Adult patients (≥18 years of age, inclusive at the time of signing the informed consent) with histologically confirmed diagnosis of metastatic or recurrent STS (histopathology, i.e., type of sarcoma and grade needs to be recorded).
2. Patients for whom treatment with doxorubicin is considered to be appropriate (hemoglobin > 10 g/dL, ANC > 1000/μL^3, and platelets > 100,000/μL^3), serum bilirubin < 1x the institutional upper limit of normal (ULN) (unless known Gilbert's disease), AST or ALT < 3x institutional ULN, and creatinine clearance ≥50 mL/min as determined by the Cockcroft-Gault equation. The laboratory normal ranges for clinical laboratory tests must be sent to the Sponsor/CRO before the study is initiated at each site.
3. Left ventricular ejection fraction ≥ 50%.
4. Disease that is considered measurable according to RECIST v1.1.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
6. Anticipated life-expectancy of at least 6 months.
7. For females of reproductive potential the following are considered highly effective acceptable forms of contraception: surgical sterilization (tubal ligation); total abstinence from sexual intercourse with the opposite sex; established hormonal birth control (e.g., oral, transdermal, injection, or implant) plus a barrier method or a double barrier method (intrauterine device, spermicide, or diaphragm plus condom) for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional month after the last dose of NOX66 or 6 months after the last dose of doxorubicin, whichever is longer.
8. For males of reproductive potential: vasectomy or use of highly effective contraception (e.g., condoms, abstinence) during the study and until 3 or 6 months after the last dose of NOX66 or doxorubicin, respectively, whichever is longer.

9.3 EXCLUSION CRITERIA

Patients who meet any of the following criteria will be disqualified from entering the study:

1. Histologically or cytologically confirmed Kaposi's sarcoma, gastrointestinal stromal tumor (GIST), extra-skeletal myxoid chondrosarcoma, epithelioid hemangioendothelioma, and desmoid tumor.
2. Hepatic impairment defined as serum bilirubin > 1x ULN (unless known Gilbert's disease) or either AST or ALT > 3x institutional ULN.
3. Unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months before study entry.
4. Untreated metastases to the CNS.
5. Received previous treatment with anthracyclines and anthracenediones.

6. Previous radiation therapy to the mediastinal or pericardial area.
7. A known allergy to any of the treatment components.
8. Active or chronic infection with human immunodeficiency virus (HIV). NOTE: Patients with chronic HIV infection, on ongoing treatment with anti-viral medications, who have an undetectable viral load are not considered to be infectious and can be included in this study.
9. Pregnant (positive urine pregnancy test) or lactating.
10. Patient not willing to use suppositories.
11. Patients with a colostomy.
12. Patients who have had a colectomy (total or left hemicolectomy) with re-anastomosis
13. Patients for whom administration of the suppositories are likely to cause pain (e.g., inflamed hemorrhoids, fissures, or lesions of the anus or rectum).
14. Patients with fecal impaction, chronic idiopathic constipation, or chronic diarrhea or alternating irritable bowel disease.
15. Patients with inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis).
16. Previous treatment with an investigational agent or the non-approved use of a drug or device within 4 weeks before study entry.
17. Uncontrolled diabetes mellitus.
18. Patients who require concomitant use of inhibitors or inducers of CYP3A4, CYP2D6 or P- glycoprotein (P- gp).

9.4 STUDY WITHDRAWAL CRITERIA

Patients will be withdrawn from the study if any of the following occurs;

- Patient withdraws consent
- Death

9.5 TREATMENT WITHDRAWAL CRITERIA

Treatment with NOX66 or doxorubicin will be withdrawn if one or more of the following occurs:

- Disease progression based on RECISTv1.1
- An inter-concurrent illness that prevents further administration of NOX66
- An adverse event that is intolerable to continue the treatment with NOX66 and doxorubicin or any DLT (Section 8.3) that has not resolved to Grade 1.
- Cardiac toxicity, e.g., if there is an absolute decrease in left ventricular ejection fraction (LVEF) of >10% from the previous evaluation, or if the actual LVEF decreases to ≤40%, requires doxorubicin to be discontinued. Doxorubicin must also be discontinued if the patient develops Grade 3 or 4 left ventricular systolic dysfunction (symptomatic congestive heart failure).
- Any other reason the Investigator considered that impacts the patient's safety.

In all cases, the reason for study or treatment withdrawal, either at the patient's request or at the Investigator's discretion, and the date of last dose of NOX66 and doxorubicin, must be recorded in the electronic case report form (eCRF) and in the patient's medical records. The patient must be followed to establish whether the reason was an adverse event causally related to NOX66, and, if so, this must be reported in accordance with the procedures in Section 11.3.

Any patient who appears to be noncompliant should be counselled but not withdrawn from the study in Cycles 2 to 6.

10 STUDY MATERIALS

10.1 STUDY PRODUCT

10.1.1 INVESTIGATIONAL PRODUCT FORMULATION AND DESCRIPTION

NOX66 is idronoxil formulated in two strengths in a proprietary lipophilic base to yield suppositories with a nominal weight of 2.2 or 3.3 g containing either 400 or 600 mg drug substance, respectively.

10.1.2 INVESTIGATIONAL PRODUCT PRESENTATION, STORAGE AND HANDLING

NOX66 is packaged with each suppository individually sealed in plastic packaging and boxed as quantities to meet the need of the treatment cycles under investigation. The drug product is stored refrigerated (2 – 8 °C). For each treatment period and cycle, the appropriate number of suppositories will be dispensed with at least enough for 1 extra day of treatment to account for misplaced or lost study drug.

10.1.3 INVESTIGATIONAL PRODUCT LABELLING

NOX66 suppositories will be packaged by the Sponsor and supplied in an open label basis. The primary plastic container which contains the suppository units will be labelled as follows: 1) Sponsor's name and address, 2) Study number, 3) Name of the product, 4) Lot Number, 5) Re-assay date, 6) Storage conditions, 7) Dosage and 8) Caution Statement: "New Drug--Limited by Federal (or United States) law to investigational use." The plastic container will be packaged in a box.

10.1.4 DOXORUBICIN, GROWTH FACTORS, DEXRAZOXANE

For details on doxorubicin see Section 8.2. The use of growth factors and dexrazoxane is permitted to reduce myelosuppression and cardiac toxicity due to doxorubicin. Growth factors may be used to treat neutropenia and thrombocytopenia in all cycles in the Dose Escalation and Expansion Cohorts (except for Cycle 1 in the Dose Escalation Cohorts). The degree of myelosuppression may be increased at Cycles 5 and 6 with the use of dexrazoxane. Doxorubicin should be given within 30 minutes after beginning the infusion with dexrazoxane. [Note: For breast cancer patients, dexrazoxane is recommended when doxorubicin cumulative dosage is ≥ 300 mg/m^2].

These products will be obtained as standard of care and are prescribed based on the Investigator's clinical judgement.

10.2 INVESTIGATIONAL PRODUCT ADMINISTRATION

10.2.1 ADMINISTRATION

Depending on the cohort/dose level, 2 to 3 suppositories will be self-administered daily for 7 days in the Monotherapy period (only for Dose Escalation part) and/or in combination with doxorubicin for the treatment cycles. In this study, the dosage forms will be inserted rectally either twice (12 hours apart) or three times (8 hours apart) per day. In patients who have regular bowel movements (i.e. within several hours after awakening) patients will be instructed to insert the suppository after the bowel movement. To promote regular movements, patients should be encouraged to consume a high fiber diet, with adequate amounts of water. In those patients who are not on a regular bowel movement schedule, insertion of the suppository should occur at regularly scheduled times individualized for the patient. If defecation occurs after NOX66 administration, no re-dosing is required. The next dose should be administered at the scheduled time. During the NOX66 and doxorubicin combination treatment cycles, if diarrhea occurs, the Investigator must follow standard management practices to manage the diarrhea to allow for NOX66 administration.

If any patients have difficulty with administering suppositories three times per day (8 hours apart) due to any personal reasons, dosing schedule can be changed to two times daily (3 suppositories per day) after Cycle 2. In this instance, patients can administer one 600-mg suppository in the morning and two 600-mg suppositories in the evening. While two suppositories are administered, each suppository needs to be inserted at least 5 minutes apart.

The dosing time for each suppository must be recorded by the patient in a diary which must be brought to the clinic at each visit. The dose escalation scheme is presented in Table 1

Proposed Starting Dose and Dose Escalation Scheme for NOX66

Table 1 Proposed Starting Dose and Dose Escalation Scheme for NOX66

Cohort	1	2	3
Increment	NA	50%	50%
Total daily dose (mg)	800	1200	1800
Daily regimen (mg)	400 BID	600 BID	600 TID

10.2.2 DURATION OF THERAPY

In the Dose Escalation part of the study, the duration of therapy for NOX66 alone is one week. After an off-treatment for 5 days, combination therapy with doxorubicin will be initiated and on Day 1 of Cycle 1, NOX66 will be administered at the same dose level as in the Monotherapy period. Doxorubicin (75 mg/m^2) will be administered on Day 2 of Cycle 1. This is followed by an off-treatment period of 2 weeks and then Cycle 2 will be initiated in the same manner as

for Cycle 1. Up to 6 cycles of doxorubicin can be administered and up to 7 weeks of NOX66 can be administered during this study.

For the Dose Expansion Cohort, patients will enter Cycle 1 of combination therapy and receive NOX66 for 7 days and on Day 2 they will receive doxorubicin. This will be followed by a 2-week rest period before starting the next cycle with a maximum number of 6 cycles.

10.2.3 DOSE MODIFICATIONS

The dose of doxorubicin can be reduced from 75 to 60 mg/m^2 if a Grade 2 toxicity related to doxorubicin occurs. If serum bilirubin is 1.2-3.0 mg/dL prior to a cycle, a 50% dose reduction of doxorubicin is recommended. If serum bilirubin is 3.1-5.0 mg/dL prior to a cycle, a 75% dose reduction of doxorubicin is recommended.

If a perineal and/or anal rash develops (Grade 1-2), a topical hydrocortisone containing haemorrhoid cream/ointment and/or cutaneous cream should be used. For Grade 3-4 perineal and/or anal rash, NOX66 treatment should be delayed until the rash resolves to Grade 1 or completely. NOX66 should also be delayed if there is proctitis, rectal mucositis, or ulcer of Grade 2 or higher. Treatment may be resumed when toxicity decreases to Grade 1. Treatment with NOX66 should also be delayed in the presence of anorectal infections and may be resumed after they are resolved.

All dose delays for NOX66 and doxorubicin need to be discussed with the Medical Monitor.

For patients developing neutropenia, the following guidelines should be used for doxorubicin dose modification.

Toxicity	**Recommended Dose Modification**
ANC < 1,000	No doxorubicin administered; treatment cycle delayed
≥ Grade 3 neutropenic fever/infection	Approximately 60 mg/m^2 doxorubicin
≥ Grade 4 neutropenia lasting longer than 1 week	Approximately 60 mg/m^2 doxorubicin
Second incidence of either: 1) ≥ Grade 3 neutropenic fever/infection 2) Grade 4 neutropenia lasting longer than 1 week	Second dose reduction to 45 mg/m^2
Reversible Grade 3 neutropenia with fever/infection or Grade 4 ANC	Retreatment with doxorubicin at Investigator's discretion

Abbreviation: ANC = absolute neutrophil count

In the event of cardiac toxicity (e.g., if there is an absolute decrease in LVEF of >10% from the previous evaluation, or if the actual LVEF decreases to ≤40%) doxorubicin must be discontinued. Doxorubicin must also be discontinued if the patient develops Grade 3 or 4 left ventricular systolic dysfunction (symptomatic congestive heart failure).

Patients who discontinue doxorubicin after 4 cycles of treatment should complete the remaining 2 cycles of NOX66 as planned. If doxorubicin is discontinued prior to 4 cycles, NOX66 treatment may continue in consultation and agreement with the Medical Monitor.

10.3 ACCOUNTABILITY FOR CLINICAL SUPPLIES

The Investigator or designee will be responsible for the dispensing, inventory, and accountability of all clinical supplies, exercising accepted medical and pharmaceutical practices at his/her institution. 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 unused medication along with the medication box will be collected and retained until the drug accountability is performed by a Sponsor representative. Once all drug accountability has been performed the Investigator will destroy NOX66 as per Site Pharmacy SOPs and/or return all remaining clinical supplies to the Sponsor who will destroy the study drug on the site's behalf. Under no circumstances will the Investigator or other staff members allow NOX66 to be used other than as directed by this protocol.

10.4 CONCOMITTANT THERAPIES

Medications (prescription and non-prescription, including vitamins and supplements) taken for the treatment of stable chronic conditions within 30 days before Screening will be recorded. All concomitant medications will be recorded on the eCRF. Every effort will be made to keep the daily dose of the concomitant medications needed for the treatment of chronic conditions during the NOX66 monotherapy and combination with doxorubicin unchanged throughout the study. Treatment of acute conditions will be made as medically indicated (e.g., infection). Growth factor support can be administered during any combination cycle, except during Cycle 1 in the Dose Escalation Cohorts. Anti-emetics are permitted prior to the administration of doxorubicin.

The following medications and products will be prohibited:

- Inducers (phenobarbital) and inhibitors (valproic acid, probenecid, atazanavir, gemfibrozil, indinavir) of Phase II drug metabolizing enzymes are prohibited within 14 days prior to first dose of NOX66 and during the combination treatment period.
- Strong inducers and inhibitors of cytochrome P450 CYP3A4, CYP2D6, and P-gp within 14 days prior to first dose of doxorubicin and during the combination treatment period. If patients are already taking these medications at Screening every effort should be made to switch to an alternative medication that does not inhibit these enzymes within 14 days prior to the first dose of doxorubicin.
- Doxorubicin is a moderate CYP2B6 inhibitor and, therefore could potentially increase the pharmacological effects of drugs that are CYP2B6 substrates (e.g., promethazine, propofol,selegiline).http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Doxorubicin_monograph.pdf

- Based on in vitro data, idronoxil may inhibit the activity of CYP2C8, 2C9, 2C19 and 3A4 enzymes in human microsomes in a range of 0.457–3000 µM and concomitant medication that is metabolized by these enzymes should be used with caution.
- A list of known inhibitors and inducers of CYP450 enzymes is provided in Section 22.3.
- Food or beverages that could potentially interfere with P-gp transport, such as those containing, but not limited to, grapefruit, Seville orange, tangerine, mango, guava, or watercress; and those that could potentially interfere with CYP3A, such as those containing, but not limited to, grapefruit juice, grapes, cranberry, pomegranate, mango, black raspberry, or black mulberry, should not be consumed 14 days prior to the first dose of NOX66 and during the study. Examples of drugs that can inhibit P-gp include cyclosporine, ketoconazole, quinidine, reserpine, ritonavir, tacrolimus, and verapamil. Inducers of P-gp activity include rifampicin, carbamazepine, St. John's wort, and tipranavir.

11 STUDY PROCEDURES AND FLOW CHART

11.1 OUTCOME MEASURES

11.1.1 PRIMARY ENDPOINTS

Safety parameters will be expressed as change from baseline, mean and median values (when appropriate) and include the following:

- Adverse events and concomitant medications
- Electrocardiogram (ECG parameters [obtained by standard 12-lead recordings], including clinically significant abnormalities in ECG rhythm and waveform morphology reported as TEAEs,
- Changes in echocardiographic parameters
- Brain type natriuretic peptide (BNP) and troponin I levels
- Clinical laboratory assessments to include serum chemistry, hematology, and urinalysis
- Vital signs (blood pressure, pulse, respiration rate, body temperature)
- Physical examination findings

11.1.2 SECONDARY ENDPOINTS

11.1.2.1 Pharmacokinetics

Blood concentrations of idronoxil and idronoxil metabolites and plasma concentrations of doxorubicin and doxorubicinol will be assayed by validated methods by a central laboratory. PK parameters of idronoxil and metabolites, will be determined using non-compartmental analyses after administration of idronoxil on Days 1 and 7 during monotherapy in the Dose Escalation Part and include:

- C_{max} Maximum observed blood drug concentration
- T_{max} Time to reach C_{max}

- AUC_{-last} Area under the blood concentration time curve (AUC) from time 0 to the last measurable concentration
- $AUC\tau$ AUC from time 0 to end or dosing interval (τ)
- AUC_{inf} AUC from time 0 to infinity (if possible)
- kel[a] Terminal elimination rate constant, calculated from a semi-log plot of the blood concentration versus time. The parameter will be calculated by linear least squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., 3 or more nonzero blood concentrations).
- $T_{1/2a}$ Terminal elimination phase half-life, calculated as 0.693/kel (if possible)

[a]Note: No value for kel, or $T_{1/2}$ will be reported for cases that do not exhibit a terminal log linear phase in the concentration versus time profile. Additional blood PK parameters may be calculated if deemed appropriate.

For the Dose Escalation Part, during the combination cycles, 1 to 4 PK samples will be obtained on Days 2, 7, and 8 to assess concentrations of idronoxil and metabolites or doxorubicin and doxorubicinol. For the Dose Expansion Part, 1 to 3 PK samples will be obtained on Days 2 and 7 to assess concentrations of idronoxil and metabolites or doxorubicin and doxorubicinol. Comparisons will be made to assess the degree of inter-and intra-patient variability during the study.

At the discretion of the Sponsor, non-evaluable concentrations or parameters may be excluded from the final PK analysis dataset. Any data exclusions will be documented in the final study report. The relationship between PK parameters and adverse events and other safety findings will be explored.

11.1.2.2 Efficacy (Secondary Analysis)

Tumor response will be assessed by RECISTv1.1 criteria (21) at the end of Cycles 2, 4 and 6 and at Months 6, 9 and 12 and at the End of Study to determine:

- Disease Control Rate ((SD+PR+CR)/All)
- Objective Response Rate [ORR]((PR+CR)/All)
- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)

The following time to event endpoints will also be assessed:

- Progression free survival (PFS)
- Overall survival (OS)

11.1.2.3 Quality of Life (Secondary Analysis)

These values will be expressed as change from baseline.

- European Organization for Research and Treatment of Cancer: Core Quality of Life Questionnaire v3.0) (EORTC QLQ-C30)
- Fatigue Severity Scale (European Organisation for Research and Treatment of Cancer: Cancer Related Fatigue Module - EORTC QLQ-FA12) Brief Pain Inventory – Short Form (BPI-SF)

11.1.2.4 Exploratory Analysis

Factors which may contribute to the overall response to the combination of NOX66 and doxorubicin will be evaluated and include.

- NOX66 dose or exposure
- Doxorubicin exposure
- Histopathology
- Cytokine and chemokine response
- ENOX2 response
- Specific genetic mutations
- Lipidomic profiling (capturing over 300 lipid species as determined by liquid chromatography-tandem mass spectrometry)
- Suppository Acceptance Questionnaire

For the safety and efficacy parameters, these are the standard measures used to assess the effects of a novel chemotherapeutic agent alone and in combination with a cytotoxic agent like doxorubicin. The safety profile of doxorubicin is well known and greater myelosuppression, or unexpectedly elevated levels of AST, ALT, and bilirubin than what one would expect with this agent given alone is suggestive of an additive effect from NOX66. The assessments of cardiac function with echocardiograms and biomarkers BNP and troponin 1 are well established to detect potential doxorubicin induced cardiac toxicity.

11.2 RECRUITMENT

METHOD ASSIGNING SUBJECTS TO TREATMENT GROUPS

Patients will be recruited from several sites in the US and Australia that are referral centers for patients with STS. Sites must confirm with Sponsor/CRO before consenting any patient on slot availability for Dose Escalation Cohorts. Once eligibility is confirmed by the Investigator or designee via a Patient Enrollment Form, the next available patient number will be assigned within a cohort (Section 12.1). The Investigator must not prescribe or administer the study drug until the patient's enrollment is approved by Sponsor/CRO, informed consent has been signed, and the patient has been assigned to a cohort.

The Sponsor/CRO will maintain a log of the number of patients at each dose level, the duration of treatment, and whether a DLT has developed and its resolution.

11.2.2 TREATMENT DISCONTINUATION

Patients will be discontinued from the study treatment if any of the following occurs as noted in Section 9.5.

- Disease progression based on RECISTv1.1
- An inter-concurrent illness that prevents further administration of NOX66
- An adverse event that is intolerable to continue the treatment with NOX66 and doxorubicin or any DLT (Section 8.3) that has not resolved to Grade 1.
- Any other reason the Investigator considered that impacts the patient's safety.

For the patients who discontinue treatment, they will continue on study for follow-up visits for tumor evaluation. All anti-cancer treatments should be recorded in the eCRF. In those patients who have evidence of disease progression during the combination of NOX66 and doxorubicin, additional tumor evaluation assessments are not needed.

If a patient is withdrawn from the study at any time, either at his/her request or at the Investigator's discretion, regardless of the reason, the Investigator will record on the relevant page of the eCRF the reason(s) for withdrawal and the day of last dosing. The eCRF (and the clinical study report) will include reasons for patient withdrawals, as well as other details relevant to the patient's withdrawal.

Any patient who appears to be noncompliant from Cycles 2 to 6 should be counselled but not withdrawn from the study. Patients who discontinue for non-safety related reasons or for noncompliance prior to the end of Cycle 1 in the Dose-Escalation Part can be replaced.

Should any patient withdraw or be withdrawn from the study prior to the completion of the Month 18 follow-up visit, every effort should be made to complete the assessments at the End of Study (Section 11.6.2.12). Patients experiencing adverse events should be followed until the AE has resolved, stabilized, or is no longer deemed clinically significant, as judged by the Investigator. Appropriate supportive and/or definitive therapy will be administered as required.

Discontinuation due to treatment failure, as defined by disease progression, is to be expected since doxorubicin is not curative for sarcoma and the optimal dose and dose frequency is not known for NOX66. Alternate treatments for sarcoma may be offered to the patient.

11.3 STUDY PROCEDURES

This study will be conducted in three parts each with screening, treatment and follow up periods as outlined in Table 2. In the Dose Escalation Part, patients receive NOX66 monotherapy followed by NOX66 and doxorubicin combination therapy. In the Dose Expansion Part, patients receive NOX66 and doxorubicin combination therapy only. Patients in each part will be followed post therapy for about 14 months. An overview of phases of the study by period is shown below (Table 2 and Figure 1).

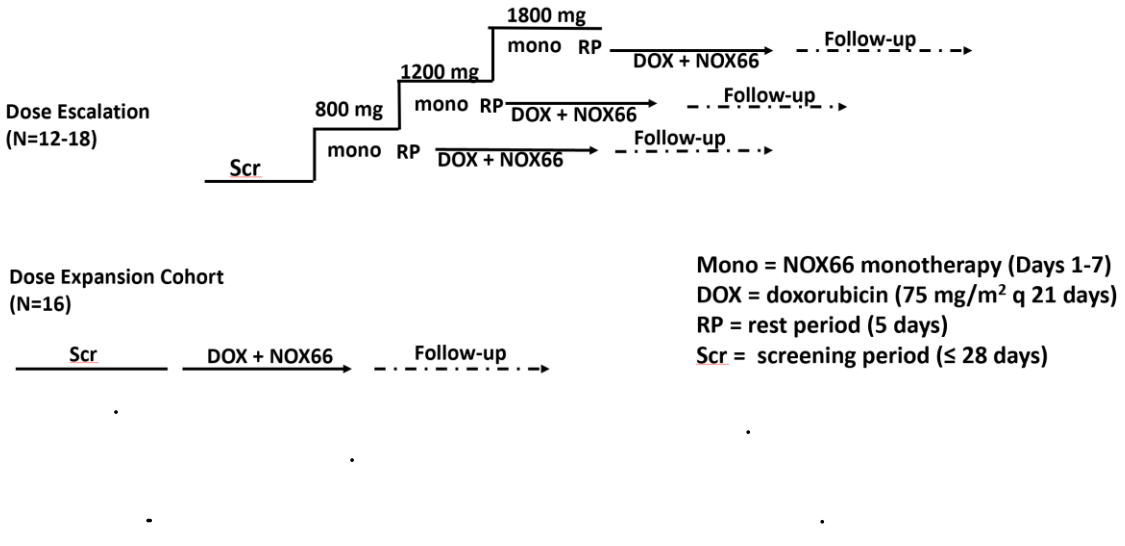
Table 2 Treatment Periods

	Dose Escalation Only		**Dose Escalation & Dose Expansion**					
				Follow-Up from C1D1				
Screening	**Monotherapy**	**Washout**	**Combination Treatment Cycles[#] 6 Cycles X 21 Days**	**Month 6 (6 M from C1D1)**	**Month 9 (9 M from C1D1)**	**Month 12 (12 M from C1D1)**	**Month 15 (15 M from C1D1)**	**Month 18 EOS (18 M from C1D1)**
28 days	7 days	5 days	126 days	1.8 M from C6D21	3 M from last f/u	3 M from last f/u	3 M from last f/u	3 M from last f/u
	12 days		**4.2 Months**	**1.8 Months**	**3 Months**	**3 Months**	**3 Months**	**3 Months**
1.3 Months			**18 Months**					
~ 20 Months								

C1D1 = Cycle 1 Day 1; EOS = End of Study; f/u = follow-up, M = month

[#]Each combination therapy cycle is 21 days with NOX66 administered on Days 1-7 at a fixed dose and regimen. On Day 2 doxorubicin is administered intravenously for 15 minutes at 75 mg/m^2. No treatment is administered on Days 8-21. During the follow-up period, neither NOX66 or doxorubicin is administered, but other approved or investigational medication for sarcoma may be administered.

Figure 1 Study Schematic



11.4 CLINICAL ASSESSMENTS

11.4.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

At Screening, demographic and other baseline characteristic will be obtained and include age, body weight, height, physical examination, medical and surgical history (with pathology review of histology of STS), ECOG performance status, concomitant medication, computer tomography/magnetic resonance imaging (CT/MRI) scans to identify measurable tumors.

11.4.2 SAFETY

Safety assessments (vital signs, physical examinations, change in concomitant medication, ECG recordings, AEs, clinical laboratory results (hematology, biochemistry, and urinalysis)) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 4). Additional tests may be done when required.

11.4.2.1 Vital Signs

Vital signs (blood pressure, heart rate, oral temperature, respiratory rate) will be assessed after single doses of NOX66 as well as after multiple doses in the NOX66 monotherapy period and prior to each dose of doxorubicin. All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same non-dominant arm for the duration of the study.

Vital sign measurements will be repeated manually if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate or heart rate measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant out-of-range vital sign measurements must be recorded as AEs.

11.4.2.2 Physical Examination

Complete physical examinations (general appearance, skin, HEENT including heart, lungs, abdomen, cervical and axillary lymph nodes, extremities, neurological, musculoskeletal systems and perineal and anal region) will be performed at Screening (Days -28 to -1), at Monotherapy Day 1 and Day 7, at the beginning of each treatment cycle and at the end of Cycle 6 (or Early Termination). Physical examinations will be performed by a medically qualified individual. In addition, medical history will be recorded at screening and prior to first dose of NOX66.

Symptom-driven limited physical examinations will be performed as clinically indicated at any study visit. All changes that are not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Physical examination can be performed 1 day prior to the scheduled visit day.

11.4.2.3 Cardiac Monitoring

A 12-lead ECG after 5 minutes of rest in the supine position will be obtained at Screening. In the Dose Escalation Cohort, triplicate 12-lead ECGs in close succession at least 1 minute apart will be obtained after 5 minutes of rest in the supine position at -0.75, -0.5 and -0.25 hours prior to administration of NOX66 and at 1, 2, 5, and 8 hours after the first dose of NOX66 monotherapy (Day 1).

On Day 7 of Monotherapy, 12-lead ECGs will be recorded performed in triplicate in the same manner and time points as on Day 1. In addition, Holter monitoring, will be conducted from 8 to 24 hours post NOX66. On Day 2 of Cycle 1, the same evaluation will be done before and after administration of NOX66, and Holter monitoring will be performed from 8 to 24 hours after NOX66 administration (Dose Escalation and Dose Expansion Cohorts). On Day 2 of Cycles 2 to 6, (combination of NOX66 and doxorubicin), triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.25 hours prior to and at 1, 2, 5 and 8 hours post morning dose of NOX66.

On days when serial ECG readings occur, before electrodes are removed after the initial reading, the electrode position is to be marked on the skin with indelible ink and the same electrode position used for all subsequent ECGs for each patient.

The following windows are acceptable for performing the ECGs:

- +/-5 minutes for pre-dose ECGs required at -0.75, -0.5 and -0.25 hours prior to NOX66 administration.
- +/-10 minutes for post-dose ECGs required at 1 hour and 2 hours after NOX66 administration.
- +/-15 minutes for post-dose ECGs required at 5 hours and 8 hours after NOX66 administration.

Echocardiography will be assessed at the start of Cycles 3, 5 and at the end of Cycle 6 (or Early Termination), and compared to baseline (Screening).

If clinically indicated, an additional echocardiograph will be done at Cycle 1 prior to the first dose of doxorubicin. All clinically significant findings that are not present at baseline should be reported as AEs.

Echocardiogram assessment can be performed 1 day prior to the scheduled visit day.

For any patient with an absolute decrease in LVEF of >10% from the previous evaluation, or if the actual LVEF decreases to ≤40%, or ≥ Grade 3 LV systolic dysfunction, doxorubicin must be discontinued and echocardiograms are to be performed at 6-month intervals in the post treatment phase.

11.4.2.4 Clinical Laboratory Tests

Laboratory assessment samples (Table 3) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 4). Clinical laboratory tests (hematology, clinical chemistry, urinalysis) will be assessed after 7 days of NOX66 monotherapy and will be compared to baseline.

Assessments of hematology, clinical chemistry, and urinalysis are to be performed prior to administration of NOX66 on Day 1 of each Cycle. Hematology and clinical chemistry will also be performed on Days 9 and 16 of Cycles 1 to 6, to determine if myelosuppression or other toxicity has occurred with either NOX66 or the combination of NOX66 and doxorubicin. Prior to each treatment cycle, the same clinical laboratory tests are to be repeated to determine if NOX66 can be administered (ANC > 1000/$\mu L^{3)}$, and to determine if the dose of doxorubicin is to be delayed or reduced if a Grade 2 or higher toxicity is present or Grade 1 or higher serum bilirubin levels are present.

Clinical laboratory tests required at Day 1 of Monotherapy and Day 1 of each cycle can be performed 1 day prior to the scheduled visit day.

At screening, renal function will be assessed by the Cockcroft and Gault formula as noted below:

Creatinine clearance (mL/min) = {(140–age(years) x weight(kg)/(72 x serum creatinine (mg/dL)} x 0.85 (if female).

Table 3 Clinical Laboratory Assessments

Hematology	**Serum chemistry**	**Urinalysis (dipstick)**
Haematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Red blood cell (RBC) count White blood cell (WBC) count with differential Platelet count	Albumin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Blood Urea Nitrogen (BUN) Bilirubin (total and direct) Carbon dioxide (CO_2) Creatinine Sodium Potassium Chloride Calcium Phosphate Magnesium Gamma--glutamyl transpeptidase (GGT) Glucose Lactate dehydrogenase (LDH) Total cholesterol Total protein Triglycerides Uric acid	pH Protein Glucose Blood Ketone bodies Specific gravity Urobilinogen Microscopy if needed based on dipstick result
Coagulation (Screening Only)		**Pregnancy Tests**
Prothrombin time (PT)/INR Activated partial thromboplastin time (PTT)		Urine human chorionic gonadotropin

Blood samples will be analyzed at a local laboratory. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated by a local laboratory. All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the Investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

Adverse events (Section 16) and concomitant medications will be recorded throughout the entire study.

11.4.2.5 Other Laboratory Tests

Plasma levels of BNP and troponin 1 will be measured prior to the first dose of NOX66, Day 7 of monotherapy and at the beginning of Cycles 1, 3 and 5 and at the end of Cycle 6.

Blood samples for chemokines and cytokines will be collected prior to the first dose of NOX66*, Day 7 of Monotherapy period (only for Dose Escalation) and at the beginning of Cycle 3 and at the end of Cycle 6.

Blood samples for genetic mutation assessment will be collected prior to the first dose of NOX66* and at the end of Cycle 6 (or at Early Termination if this occurs prior to Cycle 6).

Blood samples for immuno assays will be collected prior to the first dose of NOX66*, Day 7 of Monotherapy (only for Dose Escalation) and at the beginning of Cycle 3 and at the end of Cycle 6.

*These samples can be collected during screening period instead of Day 1 if needed, after confirming subject eligibility and providing signed informed consent.

Archived tissue sample (10 unstained slides) will be collected, if available, for immunohistopathology analysis.

The Sponsor may use any leftover samples to perform additional analyses for relevant biomarkers in the future. Taking part in this future research is optional. Patients will be asked to consent to their samples being stored and used for this optional future research.

11.4.3 PHARMACOKINETICS

Sampling timepoints for collection of blood samples for PK analyses are presented in Table 7 (Section 22.2.2.1).

Monotherapy

Following the administration of NOX66 during the Dose Escalation Part on Day 1 of Monotherapy, blood samples (1 x 4 mL) will be collected in Potassium Oxalate/Sodium Fluoride Vacutainer tubes for PK analysis of idronoxil (and metabolites) at pre-dose and at 1, 2, 3, 4, 6, 8 and 24 hours post dose. Exact times for dosing and blood sampling will be recorded. If a bowel movement occurs, during the collection period, the time of each bowel movement should be recorded, and the blood sample collections should continue as planned. The 24-hour blood sample may be collected at the patient's home by a visiting healthcare provider or in the clinic.

On Day 7 of the NOX66 Monotherapy period, blood samples will be collected for PK analysis of idronoxil from each patient, at pre-dose (within 15 minutes prior to dosing) and at 1, 2, 3, 4, 6, and 8 hours post dose. The remainder of the daily dose will be administered at 8 or 12 hours after the first morning dose of NOX66. The last PK sample will be obtained at 8 or 12 hours after the last dose of monotherapy on Day 8. The 0- to 8-hour samples must be obtained in the clinic and the samples obtained on the first day of the washout period (Day 8) will be collected at the patient's home or in the clinic. The exact time the samples are collected post dose and the time of last dose prior to collection must be recorded.

Cycle 1 (Dose-Escalation Cohort)

On Day 2, PK samples are to be collected prior to and at 1 and 2 hours post NOX66 administration and assayed for idronoxil and metabolites. For doxorubicin, blood samples (1 x 4 mL) are to be collected in K_2EDTA containing Vacutainer tubes at 0.5, 4, and 6 hours after the end of the doxorubicin infusion. On Day 7, PK samples will be obtained just prior to the morning dose of NOX66 and on Day 8 at 8 and 12 hours after the last dose on Day 7 for the TID and BID regimens, respectively. The exact times of dosing of NOX66 and doxorubicin must be recorded and when the blood samples are taken after administration of NOX66 and following the completion of the doxorubicin infusion must be recorded. The blood samples to be taken on Days 7 and 8 may be collected at the patient's home or clinic.

Cycles 2, 4, and 6 (Dose-Escalation Cohort)

On Day 2, PK samples are to be collected within 15 minutes prior to NOX66 administration and at 4 hours post NOX66 administration and assayed for idronoxil and metabolites. In addition, PK samples are to be collected at 0.5 and 4 hours after the end of doxorubicin infusion and assayed for doxorubicin and doxorubicinol (note: 0.5-hour post-dose doxorubicin PK sample is not applicable at Cycle 4).

Cycles 3 and 5 (Dose-Escalation Cohort)

On Day 2, PK samples are to be collected 4 hours after the morning dose of NOX66 in the clinic for idronoxil and metabolites concentrations. Additional PK samples are to be obtained in the patient's home just prior to the morning dose on Day 7 and on Day 8 at 8 or 12 hours after the last dose on Day 7, respectively.

Cycle 1 (Dose Expansion Cohort)

On Day 2, PK samples for idronoxil and metabolites are to be obtained, prior to NOX66 and at 4 and 6 hours post dose and prior to the morning dose on Day 7 at the patient's home. Relative to doxorubicin, PK samples are to be collected at 0.5, 4, and 6 hours after the end of the doxorubicin infusion.

Cycles 2, 4 and 6 (Dose Expansion Cohort)

On Day 2, PK samples are to be collected within 15 minutes prior to NOX66 administration and at 4 hours post NOX66 administration and assayed for idronoxil and metabolites. Samples for doxorubicin and doxorubicinol concentrations will be collected at 0.5 and 4 hours after the end of doxorubicin infusion.

On Day 2, a PK sample for idronoxil is to be collected at 4 hours after the morning dose of NOX66 in the clinic. Another PK sample is to be collected within 15 minutes prior to the morning dose on Day 7 at the patient's home.

Sampling Handling and Windows for PK Sampling

Plasma will be prepared from each blood sample within 30 minutes of collection. Details on the preparation of plasma samples are provided in Section 22.2.2.1.

The windows for PK blood sample collection are as follows:

- For pre-dose (0 hour) blood collection: 15 min before dosing
- For the 0.5 to 2-hour post dose blood collections: +/- 2 minutes from scheduled blood collection.
- For the 3- to 6-hour post dose blood collections: +/- 5 minutes from scheduled blood collection.
- For the 8- to 24-hour post dose blood collections: +/- 30 minutes from scheduled blood collection.

Pharmacokinetic blood sample collection should have priority over other study assessments. For other study assessments, in case the distribution of meals or time for study assessments coincide with the sample collection time, the sequence of events should be as follows: ECG, blood sampling, and distribution of meals. Deviations from the listed PK windows are regarded as protocol deviations.

11.4.4 EFFICACY

Treatment responses

Computer Tomography or MRI will be performed at Screening, prior to the start of Cycles 1 (only in the Dose Escalation cohorts if the previous scan was done more than 28 days previously), at the end of Cycles 2, 4, and 6, at 6, 9 and 12 months after the start of the combination therapy and at the End of Study (Month 18) or at Early Termination (ET) if the patient discontinues from the trial. Changes in the size and number of target lesions will be evaluated using RECIST v1.1 criteria, compared to baseline (Screening) or prior to Cycle 1 scan whichever is appropriate.

Other Outcome Measures

Each patient's ECOG Performance status will be assessed at the end of NOX66 monotherapy, at the start of Cycle 5 and at End of Study, compared to baseline. Assessments of pain, fatigue and QOL will be made at the end of NOX66 monotherapy (fatigue and pain only), on Day 1 of each cycle for the combination of NOX66 and doxorubicin, at Months 6, 9 and 12 of the follow-up period and at the End of Study, compared to baseline. Assessments of acceptance of suppository administration will made at the end of NOX66 monotherapy and on Day 1 of each cycle for the combination of NOX66 and doxorubicin.

11.4.5 PHARMCODYNAMICS

Changes from baseline in blood/plasma levels of cytokines, chemokines, lipids andENOX2 will be assessed on Day 7 of Monotherapy, at the beginning of Cycle 3 and at end of Cycle 6.

11.5 ASSESSMENT OF DISEASE STATUS

11.5.1 RADIOLOGIC

Computer tomography or MRI will be used to assess the size and number of all measurable target and non-target lesions as defined in RECIST v1.1. For each patient, the same modality must be used at baseline and throughout the study.

11.5.2 TREATMENT RESPONSE

Assessment of treatment response: Treatment response will be separately assessed at the end of Cycles 2, 4, and 6 and End of Study compared to baseline. The RECIST v 1.1 criteria will be used to evaluate tumor responses to determine 1) Disease Control Rate (DCR) defined as [(stable disease (SD) + partial response (PR) + complete response (CR)/All)], b) overall response rate (ORR)(PR+CR)/All), c) OS and d) PFS.

All radiologic images will be reviewed by an independent, experienced, local radiologist to assess RECIST response. The same radiologist should review each patient's scan.

11.6 STUDY VISITS

The study activities and procedures are summarized in Table 4. Details of study procedures are provided in this section. A visit schedule for the period projected from the date of first dose of study drug to the date of the final Treatment Period Visit should be established for each patient by study site staff.

11.6.1 SCREENING (DAYS -28 TO -1)

Study screening will occur approximately 2 to 28 days before Day 1. For the purposes of this study, patients will be considered enrolled when they provide signed informed consent and have met eligibility criteria. Written informed consent will be provided before any study-related procedures are performed. At screening, patients will be assigned a patient identification number and then all patients will be identified by their unique study patient number throughout the study.

The following will take place at Screening:

- Obtain informed consent by the patient prior to any study-related procedures.
- Assign patient identification number.
- Record demographics.
- Record medical/surgical history.
- Record histopathology and grade of STS.

- Obtain archival tissue samples (or 10 unstained histology slides), if available (optional). This can be collected any time during the study.
- Record prior and concomitant medications.
- Measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate and oral body temperature.
- Perform a physical examination, including body weight and height.
- Record ECOG performance status.
- Obtain a 12-lead ECG (Section 11.4.2.3).
- Perform echocardiography (Section 11.4.2.3).
- Collect urine and fasting blood samples for clinical laboratory tests (hematology, serum chemistry and urinalysis, Section 11.4.2.3). Calculate creatinine clearance using Cockcroft-Gault equation.
- Females of childbearing potential will undergo a urine pregnancy test (per inclusion criteria [Section 9.2], negative results must be obtained prior to dosing with study drug).
- Assess inclusion/exclusion criteria (Sections 9.2 and 9.3).
- Document all measurable tumor lesions with CT or MRI. If scans are available within 28 days of the first dose of NOX66 (Dose-Escalation Phase) or before Cycle 1 in Dose-Expansion Cohort there is no need for additional scans.
- Assess AEs and update medical history (Section 15.2.1).
- Patients must indicate willingness to self-administer study drug rectally. Instructions will be provided and competency in self-administration of a suppository similar in size to NOX66 must be demonstrated at the study site. Alternatively, if a given patient is accompanied by a reliable and willing household member, that individual may be trained to administer study drug to the patient and will be required to demonstrate competency at the study site.

Results of these screening evaluations will be used to determine the patient's eligibility to receive study drug according to the inclusion and exclusion criteria (Sections 9.2 and 9.3, respectively). Eligible patients who are selected and wish to continue will be scheduled to return for baseline (Day 1) assessments.

Patients who have given their informed consent, have completed all baseline evaluations, and have met all inclusion and no exclusion criteria (reconfirmed at baseline) will self-administer a single dose of NOX66 rectally.

11.6.2 TREATMENT PERIOD

The approximately 19-week Treatment Period (18 weeks for Dose Expansion Cohort) includes approximately 27 scheduled clinic visits Day 1 [baseline], Day 7 of NOX66 monotherapy (Dose Escalation part), Days 1 and 2 of Treatment Cycles 1 to 6 of combined NOX66 and doxorubicin as well as Days 9 and 16 of Cycle 1 and the other subsequent 5 cycles. Scheduled follow-up assessments will occur at Months 6, 9, 12, 15, and 18 (End of

Study) from Cycle 1 Day 1. Additional follow-up visits may be conducted at any time during study participation per Investigator's discretion based on the type and severity of any notable safety finding as well as evaluation of any doxorubicin-induced toxicity (i.e., myelosuppression) that can delay the next dose of doxorubicin or result in a dose reduction.

There is a window of ±1 day around scheduled study visits on Day 7 of NOX66 monotherapy and Day 2 of Cycles 1 to 6. A ±1 day window may also be utilized in the event of scheduling conflicts due to public holidays. A 7-day window is acceptable for all other visits during the follow-up period (Months 6, 9, 12, 15 and 18).

Telephone contact between the site staff and the patient is to be encouraged between study visits to assess compliance, tolerability of the study drug. Sufficient study drug for a 7-day period will be dispensed to the patients.

11.6.2.1 Monotherapy Period (Days 1 to 6) – Only for dose escalation

Eligible patients who are enrolled and wish to continue will return to the study site in the morning on Day 1 and the following will take place:

- Record changes in medical history including any changes in concomitant medications since screening (Section 10.4).
- Measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate and body temperature [oral or aural]; Section 11.4.2.1).
- Perform a physical examination (including weight; Section11.4.2.2).
- Obtain a triplicate 12-lead ECG after 5 minutes of rest in the supine position at -0.75, - 0.5 and -0.25 hours prior to administration of NOX66.
- Collect urine and fasting blood samples for clinical laboratory tests (Table 3). ANC should be > 1000/μL^3 prior to study drug administration.
- Collect blood samples for genetic mutations, levels of BNP, troponin I, cytokines, chemokines and immunoassays prior to NOX66 administration. (These samples can be collected during Screening, if needed, at the end of all Screening assessments)
- Females of childbearing potential will undergo a urine pregnancy test (per inclusion criteria [Section 9.2, negative results must be obtained prior to dosing with study drug). A window of -1 day is acceptable.
- Collect PK pre dose blood sample within 15 minutes prior to administration of NOX66.
- Administer questionnaires BPI-SF, EORTC QLQ-C30 and EORTC QLQ-FA12. Assess and record AEs and update medical history (Section 16).
- Review inclusion/exclusion criteria (Sections 9.2 and 9.3).

Once eligibility is confirmed, the following will occur:

- Instructions for self-administration of study drug will be reviewed with the patient and/or a household member who has agreed to administer NOX66.

- The individualized doses will be determined based on the cohort to which they are assigned. The frequency of dosing will be BID or TID beginning on Day 1.
- Patients will be given an adequate supply of study drug for 7 days administration.

The study drug will be self-administered by the patient; the patient will then undergo the following assessments:

- On Day 1, PK blood sampling at 1, 2, 3, 4, 6, 8, and 24 hours post first dose. The 24-hour sample may be taken at home or in the clinic on Day 2, prior to NOX66 administration.
- On Day 1, record triplicate 12-lead ECG at 1, 2, 5, and 8 hours after the first dose of NOX66. As noted in Section 11.4.3, ECGs are to be taken prior to the blood sample collection.
- On Day 1, assess and review TEAEs (Section 16).
- On Day 1 dispense a diary to record times of drug administration for Days 2 to 7.
- On Day 1, instruct patients to return to the study site at Day 7 with completed diary and not to take the morning dose of NOX66 on Day 7 at home.

11.6.2.2 Days 7 and 8 (±1 day) Only for Dose Escalation

- On Day 7, assess and review TEAEs (Section 16).
- On Day 7, collect urine and fasting blood samples for clinical laboratory tests (Table 3).
- On Day 7, perform a physical examination (including weight; Section 11.4.2.2).
- On Day 7, administer questionnaires BPI-SF, EORTC QLQ-FA12 and Suppository Acceptance Questionnaire (SAQ).
- On Day 7, review treatment log (diary) and assess dosing compliance.
- On Day 7, review and record concomitant medications (Section 10.4).
- On Day 7, collect blood samples for BNP, troponin 1, chemokines, cytokines and immunoassays prior to NOX66 administration.
- On Day 7, measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate and body temperature [oral or aural]; Section 11.4.2.1) prior to NOX66 administration.
- On Day 7, administer the morning dose of NOX66 in the clinic.
- On Day 7, 12-lead ECGs will be performed in triplicate at -0.75, -0.5 and -0.25 hours prior to and at 1, 2, 5, and 8 hours post morning dose of NOX66. Holter monitoring will run from 8 to 24 hours post morning dose of NOX66.
- On Day 7, PK blood sampling pre dose and at 1, 2, 3, 4, 6, and 8 hours post application.
- On Day 8, PK blood sampling at 8 or 12 hours after the last dose of NOX66 on Day 7 for those on a TID or BID regimen, respectively. These samples may be obtained by a visiting healthcare professional at home or in the clinic.

11.6.2.3 Days 9-12 (Rest Period) Only for Dose Escalation

- Document measurable tumor lesions with CT or MRI (no need to repeat if the previous scan was within 28 days prior to Cycle 1 Day 1).
- Assess and review TEAEs (Section 16).
- Review and record concomitant medications (Section 10.4).

11.6.2.4 Cycle 1

- On Day 1 collect blood for BNP and troponin 1 prior to administration of NOX66.
- On Day 1, perform a physical examination (including weight, Section 11.4.2.2).
- On Day 1 administer questionnaires BPI-SF, EORTC QLQ-C30 and EORTC QLQ-FA12.
- On Day 1, collect urine and fasting blood samples for clinical laboratory tests prior to the first dose of NOX66 (Table 3). Prior to the start of the cycle, the patient must have a minimum ANC of 1000/μL^3. On Days 9 and 16, obtain hematology and clinical chemistry values to determine if any dose-reduction or delay in doxorubicin may be needed for the next dose.
- Dose Expansion only: Females of childbearing potential will undergo a urine pregnancy test prior to dosing. A window of -1 day is acceptable.
- On Day 1, dispense sufficient supply of study drug for 7 days administration.
- On Day 1 administer the appropriate number of NOX66 suppositories/per day per assigned dose cohort and instruct the patient to take the appropriate number of suppositories on Days 2-7.
- On Day 2, measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate [to be measured over 60 seconds], and body temperature [oral or aural]; prior to the dose of doxorubicin (Section 11.4.2.1).
- On Day 2, administer doxorubicin (75 mg/m^2) over 15 minutes (or as per standard of care) at approximately 1 hour after administration of NOX66.
- On Day 2, 12-lead ECGs will be performed in triplicate at -0.75, -0.5 and -0.25 hours prior to and at 1, 2, 5, and 8 hours post morning dose of NOX66. Holter monitoring will run from 8 to 24 hours post morning dose of NOX66.
- On Day 2, PK samples are to be collected at within 15 minutes prior to NOX66 and at 1 and 2 hours (Dose Escalation only) and at 4 and 6 hours (Dose Expansion Cohort) after NOX66 administration and assayed for idronoxil and metabolites. PK samples will also be obtained at 0.5, 4 and 6 hours after the end of the doxorubicin infusion and assayed for doxorubicin and doxorubicinol.
- PK samples will be obtained within 15 minutes prior to the last morning dose of NOX66 on Day 7 (Dose Escalation and Dose Expansion Cohorts). These samples can be collected at the patients' home.
- On Day 8 PK samples will be obtained at 8 or 12 hours after the last dose of NOX66 for those on a TID or BID, regimen, respectively (Dose Escalation Cohorts). These samples can be collected at the patients' home or in the clinic.
- Review and record concomitant medications (Section 10.4).
- Assess and review TEAEs (Section 16).
- On Day 1, for those patients in the Dose-Expansion Cohort, blood samples for genetic mutations, BNP, troponin I, cytokines, chemokines and immunoassays will be obtained prior to the first dose of NOX66, if not already collected at Screening.
- Echocardiography should be repeated prior to the first dose of doxorubicin if, after the first screening echocardiograph, a patient has clinical symptoms that may indicate worsening cardiac function.

11.6.2.5 Cycle 2

- On Day 1 review treatment log, collect unused study drug, and assess compliance, from previous cycle. If needed, patients may be counseled to about being compliant with study drug.
- On Day 1, perform a physical examination (including weight, Section 11.4.2.2).
- On Day 1 administer questionnaires BPI-SF, EORTC QLQ-C30, EORTC QLQ-FA12, and SAQ. .
- On Day 1, collect urine and fasting blood samples for clinical laboratory tests prior to the first dose of NOX66 (Table 3). Prior to the start of the cycle, the patient must have a minimum ANC of 1000/μL^3. On Days 9 and 16, obtain hematology and clinical chemistry values to determine if any dose-reduction or delay in doxorubicin may be needed for the next dose.
- On Day 1, dispense sufficient supply of study drug for 7 days administration.
- On Day 1 administer the appropriate number of NOX66 suppositories/per day per assigned dose cohort and instruct the patient to take the appropriate number of suppositories on Days 2-7.
- On Day 2, measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate [to be measured over 60 seconds], and body temperature [oral or aural]; prior to the dose of doxorubicin (Section 11.4.2.1).
- On Day 2, administer doxorubicin (75 mg/m^2) over 15 minutes (or as per standard of care) at approximately 1 hour after administration of NOX66.
- On Day 2, triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.75, -0.5 and -0.25 hours prior to and at 1, 2, 5, and 8 hours post application of NOX66.
- On Day 2, PK samples are to be collected within 15 minutes prior to the morning dose of NOX 66 administration (8or 12 hours after the last dose of NOX66 on Day 1) and at 4 hours post NOX66 administration and will be assayed for idronoxil and metabolites.
- On Day 2, PK samples are to be collected at 0.5 and 4 hours after the end of the doxorubicin infusion and assayed for doxorubicin and doxorubicinol.
- Review and record concomitant medications (Section 10.4).
- Assess and review TEAEs (Section 16).
- On Day 21, assess tumor response by CT or MRI.

11.6.2.6 Cycle 3

- On Day 1 review treatment log, collect unused study drug, and assess compliance, from previous cycle.
- On Day 1, perform echocardiography (Section 11.4.2.3).
- On Day 1, collect blood for BNP, troponin 1, cytokines, chemokines and immunoassays prior to administration of NOX66.
- On Day 1, perform a physical examination (including weight, Section 11.4.2.2).
- On Day 1 administer questionnaires BPI-SF, EORTC QLQ-C30, EORTC QLQ-FA12, and SAQ.
- On Day 1, collect urine and fasting blood samples for clinical laboratory tests prior to the first dose of NOX66 (Table 3). Prior to the start of the cycle, the patient must have a minimum ANC of 1000/μL^3. On Days 9 and 16, obtain hematology and clinical chemistry

values to determine if any dose-reduction or delay in doxorubicin may be needed for the next dose.
- On Day 1, dispense sufficient supply of study drug for 7 days administration.
- On Day 1 administer the appropriate number of NOX66 suppositories/per day per assigned dose cohort and instruct the patient to take the appropriate number of suppositories on Days 2-7.
- On Day 2, administer doxorubicin (75 mg/m^2) over 15 minutes (or as per standard of care) at approximately 1 hour after administration of NOX66.
- Measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate and body temperature [oral or aural]; Section 11.4.2.1) prior to the dose of doxorubicin on Day 2.
- On Day 2, triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at 0.25 hours prior to and at 1, 2, 5, and 8 hours post application of NOX66.
- Review and record concomitant medications (Section 10.4).
- On Day 2, PK samples are to be collected at 4 hours post NOX66 administration assayed for idronoxil and metabolites.
- PK samples will be obtained just prior to the last morning dose on Day 7 (Dose-Escalation and Expansion Cohorts) and on Day 8 at 8 or 12 hours after the last dose of NOX66 on Day 7 for those on a TID or BID regimens, respectively (Dose-Escalation Cohorts only). The Day 8 samples can be collected at home or in the clinic.
- Assess and review TEAEs (Section 16).

11.6.2.7 Cycle 4

- On Day 1 review treatment log, collect unused study drug, assess compliance, from previous cycle.
- On Day 1, perform a physical examination (including weight, Section 11.4.2.2).
- On Day 1 administer questionnaires BPI-SF, EORTC QLQ-C30, EORTC QLQ-FA12 and SAQ.
- On Day 1, collect urine and fasting blood samples for clinical laboratory tests prior to the first dose of NOX66 (Table 3). Prior to the start of the cycle, the patient must have a minimum ANC of 1000/μL^3. On Days 9 and 16, obtain hematology and clinical chemistry values to determine if any dose-reduction or delay in doxorubicin may be needed for the next dose.
- On Day 1, dispense sufficient supply of study drug for 7 days administration.
- On Day 1 administer the appropriate number of NOX66 suppositories/per day per assigned dose cohort and instruct the patient to take the appropriate number of suppositories on Days 2-7.
- On Day 2, measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate and body temperature [oral or aural]; Section 11.4.2.1) prior to the dose of doxorubicin.
- On Day 2, administer doxorubicin (75 mg/m^2) over 15 minutes (or as per standard of care) at approximately 1 hour after administration of NOX66.
- On Day 2, triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.25 hours prior to and at 1, 2, 5, and 8 hours post morning dose of NOX66.
- On Day 2, PK samples are to be collected prior to the morning dose of NOX66 administration (8 or 12 hours after the last dose of NOX66 on Day 1) and 4 hours post NOX66 administration and assayed for idronoxil and metabolites.

- On Day 2, PK samples are to be collected at 0.5 and 4 hours after the end of the doxorubicin infusion and assayed for doxorubicin and doxorubicinol.
- Review and record concomitant medications (Section 10.4).
- Assess and review TEAEs (Section 16).
- On Day 21, assess tumor response by CT or MRI.

11.6.2.8 Cycle 5

- On Day 1 review treatment log, collect unused study drug, assess compliance, from previous cycle.
- On Day 1, perform echocardiography (Section 11.4.2.3).
- On Day 1 collect blood for BNP and troponin 1 prior to administration of NOX66.
- On Day 1 perform a physical examination (including weight, Section 11.4.2.2).
- On Day 1 administer questionnaires BPI-SF, EORTC QLQ-C30, EORTC QLQ-FA12 and SAQ.
- On Day 1, record ECOG status.
- On Day 1, collect urine and fasting blood samples for clinical laboratory tests prior to the first dose of NOX66 (Table 3). Prior to the start of the cycle, the patient must have a minimum ANC of 1000/μL^3. On Days 9 and 16, obtain hematology and clinical chemistry values to determine if any dose-reduction or delay in doxorubicin may be needed for the next dose.
- On Day 1, dispense sufficient supply of study drug for 7 days administration.
- On Day 1, administer the appropriate number of NOX66 suppositories/per day per assigned dose cohort and instruct the patient to take the appropriate number of suppositories on Days 2-7.
- On Day 2, measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate and body temperature [oral or aural]; Section 11.4.2.1) prior to the dose of doxorubicin.
- On Day 2, administer doxorubicin (75 mg/m^2) over 15 minutes (or as per standard of care) at approximately 1 hour after administration of NOX66.
- On Day 2, triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.75, -0.5 and -0.25 hours prior to and at 1, 2, 5, and 8 hours post morning dose of NOX66.
- On Day 2, PK samples are to be collected at 4 hours post NOX66 administration assayed for idronoxil and metabolites.
- PK samples will be obtained just prior to the last morning dose on Day 7 (all cohorts) and on Day 8 at 8 or 12 hours after the last dose of NOX66 on Day 7 for those on a TID or BID regimens, respectively (Dose-Escalation Cohorts). The Day 8 samples can be collected at home or in the clinic.
- Review and record concomitant medications (Section 10.4).
- Assess and review TEAEs (Section 16).

11.6.2.9 Cycle 6

- On Day 1 review treatment log, collect unused study drug, assess compliance, from previous cycle.
- On Day 1, perform a physical examination (including weight, Section 11.4.2.2).
- On Day 1 administer questionnaires BPI-SF, EORTC QLQ-C30, EORTC QLQ-FA12, and SAQ.

- On Day 1, collect urine and fasting blood samples for clinical laboratory tests prior to the first dose of NOX66 (Table 3). Prior to the start of the cycle, the patient must have a minimum ANC of 1000/μL^3. On Days 9 and 16, obtain hematology and clinical chemistry values.
- On Day 1, dispense sufficient supply of study drug for 7 days administration.
- On Day 1, administer the appropriate number of NOX66 suppositories/per day per assigned dose cohort and instruct the patient to take the appropriate number of suppositories on Days 2-7.
- On Day 2, measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate and body temperature [oral or aural]; Section 11.4.2.1) prior to the dose of doxorubicin.
- On Day 2, administer doxorubicin (75 mg/m^2) over 15 minutes (or as per standard of care) at approximately 1 hour at administration of NOX66.
- On Day 2, triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at- 0.25 hours prior to and at 1, 2, 5, and 8 hours post morning dose of NOX66.
- On Day 2, PK samples are to be collected at pre-dose of NOX66 administration and at 4 hours post NOX66 administration and assayed for idronoxil and metabolites.
- On Day 2, PK samples are to be collected at 0.5 and 4 hours after the end of the doxorubicin infusion and assayed for doxorubicin and doxorubicinol.

The following assessments are required at Cycle 6 Day 21, or at Early Termination if the patient discontinues the study during the treatment period:

- Collect blood for BNP, troponin 1, immunoassays, cytokines, chemokines and genetic mutation,
- Assess tumor response with CT or MRI.
- Perform a physical examination (Section 11.4.2.2).
- Measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate [to be measured over 60 seconds], and body temperature [oral or aural] (Section 11.4.2.1).
- Collect urine and fasting blood samples for clinical laboratory tests (Section 11.4.2.4).
- Administer questionnaires BPI-SF, EORTC QLQ-C30, EORTC QLQ-FA12 and SAQ.
- Perform echocardiography (Section 11.4.2.3).
- Review treatment log, collect unused study drug, and assess compliance.
- Review and record concomitant medications (Section 10.4).
- Assess and review TEAEs (Section 16).

11.6.2.10 Months 6, 9 and 12 (from Cycle 1 Day 1)

- Assess tumor response with CT or MRI.
- Single 12-lead ECG will be obtained after 5 minutes of rest in the supine position.
- Administer questionnaires BPI-SF, EORTC QLQ-C30 and EORTC QLQ-FA12.
- Review and record concomitant medications. Restrictions on concomitant medications are to be removed compared to NOX66 monotherapy and Cycles 1 to 6.
- Assess and review AEs (Section 16).
- Assess overall survival.

11.6.2.11 Months 15 (from Cycle 1 Day 1)

- Conduct telephone follow-up or chart review.
- Assess and review AEs.
- Assess overall survival.

11.6.2.12 Month 18 (from Cycle 1 Day 1) - End of Study/Early Termination

- Assess tumor response with CT or MRI, including patients who discontinue the study for progressive disease.
- Measure vital signs (blood pressure, pulse [radial or brachial (to be measured over 30 seconds if performed manually)], respiration rate and body temperature [oral or aural]; Section 11.4.2.1).
- Assess ECOG performance status.
- Collect urine and fasting blood samples for clinical laboratory tests (Section 11.4.2.4).
- Administer questionnaires BPI-SF, EORTC QLQ-C30 and EORTC QLQ-FA12.
- Perform a physical examination (Section 11.4.2.2).
- Review and record concomitant medications.
- Assess and review TEAEs (Section 16).
- Assess overall survival.

Table 4 Schedule of Procedures and Assessments for Three Periods of the Study

Procedure/Assessment / Study Day	Dose Escalation & Dose Expansion	Dose Escalation NOX66 Monotherapy Period								
	Screening	Monotherapy (Days)								Off-treatment Days
	Day -28 to Day -1	1	2	3	4	5	6	7	8	9-12
Obtain informed consent	X									
Inclusion/exclusion criteria	X	X								
Medical and surgical history[1] (including histopathology data and STS grade)	X	X								
Assess disease status (CT and/or MRI)[2]	X									X
Vital signs[3]	X	X						X		
Physical examination[4]	X	X						X		
ECOG performance status	X							X		
Hematology, clinical chemistry[5]	X	X						X		
Urine pregnancy test (WOCBP only)	X	X								
BNP, troponin I		X						X		
Blood for cytokines, chemokines, immunoassays (ENOX2)	X†	X†						X		
Genetic mutation sample	X†	X†								
Archival tissue sample (Optional)	X									
Urinalysis	X	X						X		
12-lead ECG[6]	X	X						X		
Holter monitoring[6]								X		
Dispense 7-day supply of NOX66		X								
Echocardiography	X									
Administer NOX66[7]		X	X	X	X	X	X	X		
PK samples[8]		X	X					X	X	
Record AEs	X	←					X			→
Prior & concomitant medications	X	←					X			→
Assess dosing compliance[9]								X		
Brief Pain Inventory (BPI-SF) [19]		X						X		
EORTC QLQ-C30[19]		X								
EORTC QLQ-FA12[19]		X						X		
Suppository Acceptance Questionnaire[10, 19]								X		

Procedure/Assessment / Study Day	Dose Escalation and Dose Expansion Combination of Doxorubicin and NOX66 Treatment Period Cycles 1 - 3																	
	Cycle 1[1]						Cycle 2					Cycle 3						
	1	2	3-7	8	9 & 16	21	1	2	3-7	9 & 16	21	1	2	3-7	8	9 & 16	21	
Assess disease status (CT and/or MRI)[2]											X							
Vital signs		X						X					X					
Physical examination	X						X					X						
ECOG performance status																		
Hematology, clinical chemistry	X				X[11]		X			X[11]		X				X[11]		
Urine pregnancy test (WOCBP only)	X*																	
BNP, troponin I	X											X						
Blood for cytokines, chemokines, immunoassays (ENOX2)	X*, †											X						
Genetic mutation sample	X*, †																	
Urinalysis	X						X					X						
12-lead ECG[6]		X						X					X					
Holter monitoring[6]		X																
Echocardiography	X[18]											X						
Dispense 7-day supply of NOX66	X						X					X						
Administer NOX66[12]	X	X	X				X	X	X			X	X	X				
Administer doxorubicin[13]		X						X					X					
PK samples[14]		X	X	X#				X					X	X	X#			
Record AEs[16]	←	←	←	←	←	←	←	←	X	→	→	→	→	→	→	→	→	
Prior and concomitant medications	←	←	←	←	←	←	←	←	X	→	→	→	→	→	→	→	→	
Collect unused medication, review patient log and assess compliance							X					X						
Brief Pain Inventory (BPI-SF)[19]	X						X					X						
EORTC QLQ-C30[19]	X						X					X						
EORTC QLQ-FA12[19]	X						X					X						
Suppository Acceptance Questionnaire[10, 19]							X					X						
Overall survival																		

	Dose Escalation and Dose Expansion Combination of Doxorubicin and NOX66 Treatment Period Cycles 4-6															
Procedure/Assessment / **Study Day**	**Cycle 4[1]**					**Cycle 5**						**Cycle 6**				
	1	**2**	**3-7**	**9 & 16**	**21**	**1**	**2**	**3-7**	**8**	**9 & 16**	**21**	**1**	**2**	**3-7**	**9 & 16**	**21/ET[1]**
Assess disease status (CT and/or MRI)[2]					X											X
Vital signs		X					X						X			X
Physical examination	X					X						X				X
ECOG performance status						X										
Hematology, clinical chemistry	X			X[11]		X				X[11]		X			X	X
BNP, troponin I						X										X
Blood for cytokines, chemokines, immunoassays (ENOX2)																X
Genetic mutation sample																X
Urinalysis	X					X						X				X
12-lead ECG[6]		X					X						X			
Holter monitoring[6]																
Dispense 7-day supply of NOX66	X					X						X				
Echocardiography						X										X
Administer NOX66[12]	X	X	X			X	X	X				X	X	X		
Administer doxorubicin[13]		X					X						X			
PK samples[14]		X					X	X	X#				X			
Record AEs[16]	←								X		→					
Prior and concomitant medications	←								X		→					
Collect unused medication review patient log and assess compliance	X					X						X				X
Brief Pain Inventory (BPI-SF) [19]	X					X						X				X
EORTC QLQ-C30[19]	X					X						X				X
EORTC QLQ-FA12[19]	X					X						X				X
Suppository Acceptance[10, 19]	X					X						X				X
Overall survival																X

Abbreviations: BNP = brain type natriuretic peptide; CT = computed tomography; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; ENOX2 = Ecto-NOX disulfide-thiol exchanger 2; EOS=End-of-Study; ET=Early Termination; Mo = month; MRI = magnetic resonance spectroscopy; PK=pharmacokinetics; QOL = Quality of Life; WOCBP = women of childbearing potential

Note: For days not specifically designated on the schedule of assessments, the standard of care for the individual institution will be followed, any AEs and concomitant medications will be recorded on the eCRF.

† Blood samples for chemokines, cytokines, immunoassays (ENOX2) and genetic mutation to be collected either after eligibility is confirmed at Screening, or on Day 1 just prior to the first dose of NOX66.

Dose Escalation Cohort only

*Dose Expansion Cohort only

Dose Escalation and Dose Expansion Follow-Up Period and End of Study/Early Termination					
Assessment / **Study Day**	**Follow-Up (months from Cycle 1 Day 1)**				**EOS/ET[15]**
	6	**9**	**12**	**15[17]**	**18**
Assess disease status (CT and/or MRI)[2]	X	X	X		X
Vital signs					X
Physical examination					X
ECOG performance status					X
Hematology					X
Clinical chemistry					X
Urinalysis					X
12-lead ECG	X	X	X		
Record AEs[17]	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X
Brief Pain Inventory (BPI-SF) [19]	X	X	X		X
EORTC QLQ-C30[19]	X	X	X		X
EORTC QLQ-FA12[19]	X	X	X		X
Overall survival	X	X	X	X	X

1. Full medical and surgical history will be recorded at Screening. At Day 1 monotherapy; an interim history is to be recorded prior to first dose of NOX66.
2. Standard of care imaging performed prior to informed consent but within 28-days of enrollment may be used to confirm screening requirements. Disease status will be measured by radiologic methods (CT or MRI) at Screening, prior to beginning of Cycle 1 (only for dose escalation, if the previous scan is more than 28 days), end of Cycles 2, 4 and 6, at Months 6, 9 and 12 and End of Study. No patient is permitted to start a subsequent cycle until it is confirmed that disease progression has not occurred at the scheduled imaging assessment timepoint.
3. Vital signs will include weight, body temperature, respiratory rate, radial pulse rates, and systolic and diastolic blood pressures. Height and body surface area will be recorded at Screening only.

4. Complete physical examinations will be conducted at Screening (Day -28 to Day -1), prior to the first dose of NOX66, at the start of each treatment cycle and at End of Study. Complete physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, muscular skeletal and nervous system. Abbreviated physical examinations may be conducted as needed and will focus on new symptoms and will include examination of relevant systems as identified by the Investigator. Physical examinations need to include the assessment of the perineal and anal region.
5. Hematology and chemistry assessments will be done weekly during Cycle 1 and with a window of (±2 days) during Cycle 2-6 and End of Study/Early Termination.
6. Refer to Table 8 for details. Triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.75, -0.5 and -0.25 hours prior to administration of NOX66 and at 1, 2, 5, and 8 hours after the NOX66 application on Monotherapy Days 1 and 7 (Dose Escalation patients only) and Cycle 1 Day 2 (all patients). Holter monitoring will be recorded from 8 to 24 hours post NOX66 on Monotherapy Day 7 and Cycle 1 Day 2. On Day 2 of Cycles 2 to 6, triplicate 12-lead ECGs will be obtained after 5 minutes of rest in the supine position at -0.25 hours prior to and at 1, 2, 5 and 8 hours post morning dose of NOX66.
7. Patients will receive instructions on how to use the suppository and receive an adequate number of dosage units for the assigned dose level. ANC must be > 1000/μL^3 prior to NOX66 administration.
8. In the NOX66 monotherapy, PK samples will be obtained on Day 1 at pre-dose (within 15 minutes of dosing) and at, 1, 2, 3, 4, 6, 8, and 24 hours post application. On Day 7, PK samples will be collected at pre-dose (within 15 minutes prior to dosing) and at 1, 2, 3, 4, 6, and 8 hours post application as well as on Day 1 of the Washout Period at 8, or 12 hours after the last dose of NOX66 for those on a TID or BID regimens, respectively.
9. Dosing compliance for NOX66 will be assessed weekly. Days with an abnormally high number of bowel movements are to be noted in the eCRF.
10. Suppository Acceptance Questionnaire will be used to assess how acceptable the dosage form is to the patient.
11. The additional tests for hematology and serum chemistry on Days 9 and 16 are to assess any hematological or clinical laboratory tests for DLTs and/or require a dose reduction to 60 mg/m^2 or lower (37.5 mg/m^2 or 18.75 mg/m^2 based on serum bilirubin), or a delay in initiation of another cycle of the combination. These additional hematological and clinical laboratory tests should be performed at each cycle. Visit windows are ± 2 days of the scheduled visit.
12. During combination treatment cycles, NOX66 is administered on Days 1 to 7 and doxorubicin is administered on Day 2.
13. Doxorubicin (75 mg/m^2 or reduced dose) to be given on Day 2 of each 21-day cycle.
14. For Dose-Escalation Cohorts, PK samples will be obtained at pre-dose and at 1 and 2 hours post NOX66 on Day 2 Cycle 1. PK samples for idronoxil will be obtained on Day 2 of Cycles 2, 4 and 6 at pre-dose and 4 hours post dose. Additional PK samples for idronoxil will also be obtained pre-dose on Day 7 and at 8 or 12 hours after the last dose of NOX66 on Day 7 for those on a TID or BID regimens, respectively on Cycles 1, 3, and 5. For the Dose Expansion Cohort, PK samples for idronoxil will be obtained on Day 2 of Cycles 1, 2, 4, and 6 at pre-dose and at 4 hours post NOX66 and on Cycle 1 at 6 hours post NOX66. On Cycles 1, 3, and 5 PK samples are to be collected just prior to the morning dose of NOX66 on Day 7. For doxorubicin in the Dose Escalation Cohort, PK samples will be obtained at 0.5, 4 and 6 hours after the end of infusion on Day 2 Cycle 1 and at 0.5 and 4 hours at the end of infusion on Day 2, Cycles 2, 4 and 6. For doxorubicin in the Dose Expansion Cohort, PK samples will be obtained at 0.5, 4 and 6 hours after the end of infusion on Day 2 Cycle 1 and at 0.5 and 4 hours at the end of infusion on Day 2, Cycles 2, 4 and 6 (Table 7).
15. All patients who discontinue the study early for whatever reason after the first dose of NOX66, or during treatment cycles (Cycles 1-6), will be followed up within 28 days of discontinuation and submit to assessments detailed in the column of Cycle 6 Day 21/Early Termination. Patients who discontinue the study early during the follow-up period will complete a final visit with assessments detailed in the column of End of Study/Early Termination. Patients who complete the study in full will have an End of Study visit at Month 18.
16. Adverse events to be recorded up to 30 days after the last dose of NOX66 or doxorubicin, whichever is longer.
17. Month 15 will be telephone follow-up/chart review.
18. Echocardiography should be repeated prior to the first dose of doxorubicin if, after the first screening echocardiograph, a patient has clinical symptoms that may indicate worsening cardiac function.
19. Study Questionnaires (EORTC QLQ-C30, EORTC QLQ-FA12, BPI-SF and SAQ) to be administered if available in the required language.

12 METHODS OF ASSIGNMENT OF INTERVENTION

12.1 ALLOCATION OF TREATMENT

The Investigator or designee will record key information on the patient in the eCRF to verify that the patient meets the inclusion/exclusion criteria (Sections 9.2and 9.3). The Investigator must not prescribe the study drug until the patient's enrollment is approved and the patient has been assigned to a cohort and dose level based on what is needed to complete the cohort (3 or 6 patients or more if there are discontinuations, or the dose group needs to be expanded for a particular reason). The Investigator will then dispense to the patient an adequate number of either the 400 or 600 mg suppository dosage forms to complete the NOX66 monotherapy portion of the study or a treatment cycle with doxorubicin. Each patient number will be used only once, in sequential order within a cohort as noted below.

Cohort 1	Patient Numbers 101-109
Cohort 2	Patient Numbers 201-209
Cohort 3	Patient Numbers 301-309

The patient numbers for the Dose-Expansion Cohort will range from 401-424.

12.2 BLINDING AND UNBLINDING

This is an open label study.

13 DATA COLLECTION AND MANAGEMENT

13.1 METHODS

The 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 on to the eCRFs 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 eCRF 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. Electronic CRFs will be provided by the Sponsor.

The Investigator will be responsible for the timeliness, completeness, and accuracy of the information entered on the eCRF. The 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 eCRFs. All eCRFs 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 by the Sponsor or representative during the study will be communicated to the site for prompt correction.

13.1.1 ELECTRONIC CASE REPORT FORM

All information relative to the study will be recorded on an eCRF to be supplied to the Investigator. Instructions will be provided for the completion of the eCRF. Data corrections will be automatically documented via the electronic data capture (EDC) software's "audit trail."

13.1.2 STORAGE OF DOCUMENTS

The Investigator will retain source documents and all other study related documents for 2 years after the last approval of a marketing application in an International Council for Harmonization (ICH) region or at least 2 years after the formal discontinuation of the clinical development of the investigational product.

13.2 DATA MANAGEMENT

The Sponsor or a designee/CRO will supply eCRFs. An eCRF must be completed for each patient who signs an Informed Consent Form (ICF). All data collected during the study will be recorded in this individual, patient-specific eCRF. Instructions will be provided for the completion of the eCRF. and any corrections made will be automatically documented via the EDC software's "audit trail" as described above.

Completion of the eCRF should be kept current to enable the monitor to review the patient's status throughout the course of the study. All information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood. The eCRF will be completed, reviewed, and signed off or e-signed by the Investigator. The Investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF, the data queries, and the study site notifications, and agrees with the content.

If a patient is assigned to receive NOX66 and is not treated with study drug, the reason must be recorded on the eCRF.

13.2.1 DATA CODING

Medications will be coded from the WHO Drug Dictionary and medical history and adverse events will be coded using the MedDRA (Version 22 or higher) terminology for System Organ Class and Preferred Term.

13.2.2 DATA VALIDATION

To ensure the quality of clinical data across all patients and study sites, a Clinical Data Management review will be performed on patient data according to specifications given to the CRO. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, patient data will be checked for consistency, completeness, and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

A Data Management Plan will be developed to describe all manual and electronic validation checks of the data prior to analysis.

14 STATISTICAL SECTION

14.1 SAMPLE SIZE

Up to 18 patients may be enrolled in the Dose Escalation part of this study, in cohorts of 3 or 6 patients at each specified dose. Patients must take at least 80% of their prescribed doses to be considered eligible for MTD evaluation. Sixteen patients will be enrolled in the Dose Expansion part of this study.

These sample sizes are not based on statistical considerations but are deemed sufficient to determine the MTD for and to describe the pharmacokinetic characteristics of this agent.

An expansion cohort of N=16 will allow a total sample size of up to 34 patients. If the expected response rate is 18% (6/34) for a hypothetical comparator and the expected response rate of NOX66 will be 24% (8/34) in the current NOX66-004 trial, this sample size ensures an 85% probability that the observed response rate of NOX66- will be greater than 18%.

14.2 ANALYSIS SETS

There will be two analysis sets

- Safety Set: All patients treated with at least one dose of idronoxil will be included in the Safety Set (SS). All analyses of safety, toxicity, and PK will be performed for this set.
- Full Analysis Set: All patients who complete at least one cycle of idronoxil + doxorubicin combination therapy will be included in the Full Analysis Set (FAS). Analyses of efficacy, tolerability, and biomarkers will be performed for this set.

14.3 STATISTICAL METHODOLOGY

14.3.1 GENERAL STATISTICS METHODS

All data will be summarized by idronoxil dose group. For safety analyses, a summary group consisting of all dose groups combined may also be presented.

For all measurements, the baseline value will be the last measurement taken before the first dose of study drug, whether idronoxil or of idronoxil + doxorubicin depending on the cohort.

Standard summary statistics will be presented for all measurements. For continuous variables, the standard summary statistics will be the number of observations (n), mean, standard deviation, median, minimum and maximum. For categorical variables, the standard summary statistics will be the number and percentage of observations in each category. Categories that are specified on the eCRF which contain no observations will be presented in the data summaries with a value of 0.

An AE with a completely missing start date will be assumed to start one minute after the date-time of the first idronoxil dose. If the severity of a reported AE is missing, it will be assumed that the event is severe; similarly, if the relationship of a reported AE to study treatment is missing, it will be assumed that the event is definitely related to treatment. No other missing data will be imputed. Incomplete start dates for Adverse Events and Concomitant Medications and incomplete end dates for AEs will have missing parts imputed by a conservative procedure which will be specified in the Statistical Analysis Plan (SAP).

14.3.2 DISPOSITION, DEMOGRAPHICS, AND BASELINE DISEASE CONDITION

Patient disposition, baseline demographics, and baseline disease condition will be summarized.

14.3.3 EXPOSURE TO TREATMENT

The summary of exposure will include the final idronoxil and doxorubicin doses, and the cumulative doses of idronoxil and doxorubicin received over the course of the entire study. Summaries will also be provided of the number of idronoxil treatments missed, the number of changes in the idronoxil and doxorubicin doses, the number of patients receiving dexrazoxane, and the dexrazoxane dose.

14.3.4 ADVERSE EVENTS

An AE will be deemed treatment emergent (TEAE) if it starts or worsens in severity or toxicity after the beginning of treatment, whether with idronoxil or with idronoxil + doxorubicin.

Adverse events will be coded using the MedDRA Dictionary, Version 22.0 (or higher). Treatment emergent adverse events will be summarized by MedDRA Preferred Term and System Organ Classification for each dose group. Separate summaries will be provided for TEAEs with onset prior to the first dose of doxorubicin, with onset during the first cycle of idronoxil+ doxorubicin therapy, and for TEAEs with onset after the end of the first treatment cycle.

The toxicity of an AE will be assessed by the NCI-CTCAE, Version 5.0. Summaries of TEAEs will be provided by dose group and toxicity grade. Summaries of TEAEs will also be provided by dose group and Investigator-reported severity and by dose group and Investigator-reported relationship to study treatment.

A summary will be provided of the overall incidence and the incidence of component terms for the Standardized MedDRA Queries (SMQs) for Cardiac Failure and for Cardiomyopathy.

A separate summary will be provided of Serious Adverse Events (SAEs) by dose group. Summaries will be presented for all SAEs, for treatment-emergent SAEs, for treatment-emergent SAEs that occur prior to the first dose of doxorubicin, during the first cycle of idronoxil + doxorubicin combination treatment, and after the end of the first cycle of combination treatment.

Deaths on study or within 30 days after a patient exits the study will be summarized by treatment. A listing of all deaths will be provided.

14.3.5 LABORATORY SUMMARIES

Safety laboratory results will be summarized by dose group. At each scheduled laboratory collection, the laboratory result and the change from baseline in laboratory result will be summarized for each laboratory parameter. CTC grades will be assigned to laboratory results where they are defined, and the frequency and percentage of each CTC grade will be included in the summary.

Shift tables will be provided for change in CTC grade from baseline to end of study and from baseline to worst grade on study.

Brain type natriuretic peptide measurements will be summarized using descriptive statistics at baseline and at Cycles 1, 3, 5, and the end of Cycle 6 or Early Termination (if occurs prior to the end of Cycle 6). The number and percentage of patients with BNP laboratory values greater than 500 pg/mL and with BNP laboratory values between 100 and 500 pg/mL will be presented.

Blood levels of chemokines and cytokines will be summarized using descriptive statistics at baseline, Day 7 of Monotherapy period (only for Dose Escalation), at Cycle 3, and at the end of Cycle 6 or at Early Termination (if occurs prior to the end of Cycle 6).

Listings of genetic mutations at baseline and at end of Cycle 6 or Early Termination will be made.

Blood levels of ENOX2 will be summarized using descriptive statistics at baseline, at Cycle 3, and at the end of Cycle 6 or at Early Termination (if occurs prior to the end of Cycle 6). These levels will also be assessed in the same manner for patients in the Dose Escalation Cohorts, including those on Day 7 of Monotherapy period, if the samples are collected.

14.3.6 VITAL SIGNS

Vital signs will be summarized by dose group. Descriptive statistics will be provided for each vital sign at each visit and for the change from baseline to that visit. For vital signs with an associated CTC grade, the summaries will include the number and percent of patients at each grade.

14.3.7 ECG PARAMETERS

For each ECG parameter (PR, RR, QRS, and QT intervals, and QT interval corrected for heart rate using QTcF intervals where the QT intervals corrected for heart rate by Fridericia's formula [QTcF = $QT/(RR)^{⅓}$], the parameter and the change from baseline in that parameter will be summarized at all time-points where an ECG is collected. Where triplicate ECG measurements are available, the descriptive statistics will be calculated using the arithmetic average of the three raw measurements. Holter monitoring will not assess ECG intervals but will provide information on cardiac rate and rhythms.

14.3.8 OTHER SAFETY ANALYSES

Echocardiography findings will be summarized by dose group at baseline and at Cycles 3, 5, and the end of Cycle 6 or Early Termination.

Physical exam findings will be summarized by dose group at baseline, at the start of each cycle and at the End of Study or Early Termination.

ECOG performance status will be summarized at each visit where it is collected.

14.3.9 PHARMACOKINETIC ANALYSES

Blood concentration of idronoxil and metabolites will be summarized by collection time for each dose group using descriptive statistics. Separate summaries will be provided for idronoxil blood concentrations collected on Days 1 and 7 of idronoxil monotherapy, and from pre-dose to 4 hours post dose on Day 2 of Cycles 1 to 6. Trough values will also be assessed on Days 7 and 8 of Cycles 1, 3 and 5. Blood concentrations of idronoxil after monotherapy and in combination with doxorubicin will be compared.

Plasma concentrations of doxorubicin and doxorubicinol will be summarized by collection time for each dose group using descriptive statistics.

Pharmacokinetic parameters will be summarized by descriptive statistics for each dose group for idronoxil alone on Days 1 and 7. Graphical methods may be used to assess the relationship between idronoxil and doxorubicin concentrations and QTc values and other toxicities of interest.

14.3.10 EFFICACY ANALYSES

Treatment response will be assessed by RECIST v1.1 criteria for patients in the FAS at the end of Cycles 2, 4, and 6, at the 6-month, 9-month, and 12-month follow-up visits, and at the End of Study or Early Termination. Along with CR, PR and SD, the ORR will be defined as the relative frequency of patients with either CR or PR, and the DCR will be defined as the relative frequency of patients with CR, PR, or SD.

The ORR, the DCR, and the frequencies of CR, PR, SD, and PD will be summarized at the end of Cycles 2, 4 and 6 and at the 6-month, 9-month, 12-month and up to 18-month follow-up visits. A summary will also be provided of best response on study.

At the assessment at the end of Cycle 6, a one-sided exact binomial test will be used to test the null hypothesis that the ORR is no greater than 0.20 (20%) against the alternative hypothesis that the ORR is greater than 0.20 at an approximate level $p = 0.025$. A similar test against the performance level of 0.20 will be performed for the rate of best objective response on study.

Overall survival will be defined as the time in months from initial treatment until death or censoring. Patients not known to have died at the time of analysis will be censored at the time of last contact with study personnel., including patients who are lost to follow-up. The overall survival curve will be estimated for the FAS by the Kaplan-Meier method.

Progression-free survival will be defined as the time in months from initial treatment until death, disease progression, or censoring. Patients who are lost to follow-up will be censored at the time of their last contact with study personnel. Patients who leave the study to begin an alternative therapy will be censored on their day of study discontinuation. The PFS curve will be estimated for the FAS by the Kaplan-Meier method.

14.3.11 QUALITY OF LIFE

All Quality of Life (QoL) analyses will be performed on the FAS. Scales from the EORTC-QLQ-C30and items from the Brief Pain Inventory – Short Form, EORTC-QLQ-FA12and Suppository Acceptance Questionnaire at each time point and changes from baseline will be summarized using descriptive statistics. Details of the scoring algorithms used to generate the QoL scores will be described in the SAP.

A Statistical Analysis Plan (SAP) will be developed and the analysis will be performed by a statistician using SAS {version TBD}.

14.3.12 STATISTICAL ANALYSIS PLAN

Further details on statistical methods, presentations, and rules for data handling will be provided in a Statistical Analysis Plan that shall be approved prior to the opening of the Dose Expansion Cohort.

14.4 INTERIM AND ADDITIONAL ANALYSIS

An interim analysis will be performed after all patients in the Dose Escalation cohorts have either discontinued or completed 3 treatment cycles, whichever comes first. A second interim analysis may also be performed after 50% of the patients in the Dose Expansion Cohort have either discontinued or completed 3 treatment cycles.

The results from these analyses will not be used to modify the study design or to stop the study.

15 MONITORING

15.1 MONITORING OF CASE REPORT FORMS

The study will be monitored by a CRO on behalf of the Sponsor. Monitoring will be conducted according to ICH GCP guidelines and Monitoring CRO SOPs. An initiation meeting will be conducted by CRO. At this meeting the protocol, the procedure for completing the eCRFs, and pertinent aspects of the eCRFs will be reviewed with the Investigator and all study staff.

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, patient charts, laboratory reports, X-ray reports and scans as specified in the monitoring plan. Anonymity of the patient will be maintained at all times.

Regulatory authorities, the IRB or the Sponsor may request access to patient clinical notes and other relevant study documentation for an on-site audit or inspection. The Investigator is obliged to facilitate this process by allowing full access.

15.2 SAFETY DATA MONITORING

The Medical Monitor will review and evaluate all toxicities causally associated with NOX66 alone in combination with doxorubicin in each cohort.

15.2.1 SAFETY MONITORING AND OVERSIGHT

After each cohort has completed Cycle 1, the SRC meeting will be held. The meetings will be comprised of the enrolling Investigators, a representative from the Sponsor, and may also include a cardiologist or other outside consultants at the Sponsor's discretion. The role is to assess any DLTs and adjudicate the MTD and whether the study should continue or be terminated based on efficacy, safety and tolerability data. A charter for the SRC will be developed prior to initiation of the clinical study.

If available, PK, PD, and efficacy data will also be included for review at the SRC meeting

15.2.1.1 AE Reporting

All AEs are graded according to NCI-CTCAE v5.0. AEs are captured from the time of consent and must be reported in the eCRF.

. Some events may make the patient ineligible for enrollment. Unanticipated events should be reported to the IRB, according to its requirements. Patients will be questioned at every visit after the first dose until the last follow-up visit regarding the occurrence and nature of any TEAEs. All TEAEs will be reported, whether or not they are deemed to be related to investigational product.

A description of the event or diagnosis including dates, severity, relationship to the investigational product, action taken and outcome, and whether or not the event was also serious, must be reported on the AE eCRF for each TEAE recorded in the patient's chart.

15.2.1.2 Expedited Reporting of Adverse Events

The Medical Monitor should evaluate every AE to determine if (1) the AE meets the requirements for expedited reporting and/or (2) if the AE meets the criteria for a safety pause/prompt AE review (Section 15.2.2). The Medical Monitor's contact information is provided in Section 16.2.

The study product for which expedited reporting is required is NOX66.

The Sponsor, or if designated, the CRO, will report all serious, unexpected, suspected adverse reactions observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). SAE reporting procedures are provided in Section 16.1.2.

15.2.2 SAFETY REVIEWS

15.2.2.1 Initial Safety Evaluation

Enrollment will be stepwise starting with Cohort 1 (N=3). After 3 patients complete Cycle 1 and have taken at least 80% of the target number of doses, and completed all safety evaluations, all data will be reviewed by the SRC to determine if the next cohort can be enrolled. If no DLT was observed in a cohort of 3 patients, the next cohort of 3 new patients may be enrolled at the next higher dose level.

15.2.2.2 Safety Considerations for Dose Escalation

In addition to monitoring patient's safety throughout the study period, the Medical Monitor and Investigator will participate in the SRC meeting to assess cumulative safety data available on all

patients who had received at least 80% doses to determine whether dose escalation may occur according the prespecified rules in Section 8.1.1

15.2.2.3 Safety Pause and Prompt AE Review

If a DLT occurs in 1 patient in a cohort of 3 patients at a given dose level of NOX66 + doxorubicin, then 3 more patients should be enrolled at that same dose level. If a DLT is not observed in the additional 3 patients, the next cohort of 3 new patients may be enrolled at the next higher dose level.

If DLT occurs in 2 patients in a cohort of 6 patients at a given dose level, then this dose level will be defined as the DLT dose level. All Investigators will be informed, no additional patient(s) will be enrolled at the DLT dose level, and dose-escalation will stop. No more than 6 patients should be enrolled at the DLT dose level.

The dose for the next cohort will be determined at the SRC review meeting to evaluate all the available safety (including AEs that are not DLTs).

When a DLT occurs, the site must immediately inform the CRO who will then inform the other sites that a DLT has occurred and evaluate if a second DLT has occurred at any other sites. If 2 or more DLTs occur at the same dose level, further enrollment of new patients at that dose level or higher across all sites will be suspended until the SRC meeting occurs to evaluate if the MTD has been exceeded. To be included in a dose-escalation decision or determination of MTD, an evaluable patient is defined as one who either experienced a DLT during the first 21-day treatment cycle (Cycle 1) or has not experienced a DLT and has taken at least 80% of the prescribed daily doses of NOX66 of the monotherapy period and the first 21-day treatment cycle and completed all safety evaluations required in Cycle 1.

Due to the potential for Cycle 1 discontinuations, patients withdrawing for reasons other than safety will be replaced.

When a dose escalation is stopped, the patients treated at lower doses can continue as planned.

15.3 AUDITING

Quality assurance (QA) procedures are designed to ensure complete, timely, and accurate submission of data, and that protocol requirements and complications and/or adverse events are immediately identified.

In addition to the monitoring visits outlined above, an investigational site may undergo a QA audit. Noxopharm or their authorized representatives or a regulatory agency such as the FDA may conduct the audit. If the FDA requests an audit of the study site, the Investigator is required to inform Noxopharm or the monitoring CRO immediately.

16 ADVERSE EVENT REPORTING

16.1 DEFINITIONS

16.1.1 ADVERSE EVENTS

An AE is any unanticipated or unintended medical occurrence or worsening of a sign or symptom (including an abnormal laboratory finding) or disease in a study participant, that occurs after the informed consent is obtained, which does not necessarily have a causal relationship with the study condition, procedures or study agent(s). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition (including the physical examination), or abnormal results of diagnostic procedures (including laboratory test abnormalities).

Events should also be considered AEs if they:

- result in discontinuation from the study,
- require treatment or any other therapeutic intervention,
- require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality),
- are associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact

Clinically Significant Laboratory Changes: It is the Investigator's responsibility to review the results of all laboratory tests as they become available. For each abnormal result, the Investigator needs to ascertain whether the abnormality presents a clinically significant change from baseline. If the change is due to the expected course of the patient's underlying disease (e.g. elevated cholesterol in a study of dyslipidemia), it is not considered an adverse event unless the abnormality is more severe than expected. A laboratory test may be confirmed by repeat testing or other diagnostic tests before being considered an adverse event. If the laboratory abnormality is a significant change from baseline for the patient, then it should be considered an adverse event.

An Adverse Event is not:

- a surgical procedure
- a situation where an untoward event did not occur, (e.g. an elective hospitalization)
- the disease being studied, unless progression is more severe than anticipated
- lack of efficacy
- baseline conditions that have not worsened in severity or frequency
- the puncture from venipunctures

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

All adverse events are to be followed up for 30 days post the last dose of study drug or until resolution (whichever is sooner).

Adverse events reported by the patient or observed by the Investigator will be listed individually on an adverse event form in the eCRF. The signs and symptoms, time of onset, criteria for assessing causality to study drug (Table 5) and outcome categories should be defined (Table 6).In order to classify AEs and diseases, preferred terms and system organ classes will be assigned by the Sponsor to the original terms entered on the eCRF using the Medical Dictionary for Regulatory Activities (MedDRA) (Section 13.2.1).

16.1.2 SERIOUS ADVERSE EVENTS

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

A SAE or reaction is defined as any untoward medical occurrence that results in any of the following outcomes:

- Death
- Life-threatening adverse drug experience defined as any adverse drug experience that, in the opinion of the Investigator, places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.
- An in-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity, defined as “A substantial disruption of a person’s ability to conduct normal life functions”
- Congenital anomaly/birth defect (in the offspring of a patient)

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 v1.1 criteria for solid tumors), 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 5.

16.1.3 GUIDELINES FOR DETERMINING CAUSALITY AND SEVERITY

The Investigator must assign a relationship of each adverse event to the receipt of the investigational product (NOX66 or the combination of NOX66 and doxorubicin). The Investigator will use clinical judgment to assess a plausible biologic mechanism for a temporal relationship between the onset of the event in relation to receipt of the investigational product, and the Investigator may determine possible alternate etiologies including underlying disease, concurrent illness or concomitant medications. The following guidelines should be used by Investigators to assess the relationship of an adverse event to study product administration.

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

Table 5 Relationship 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.

Hospitalization for elective surgery related to a pre-existing condition, routine clinical procedures, or social reasons that did not increase in severity or frequency after beginning the study are not considered to be AEs but must be recorded in the source documents. If the hospitalization is due to a pre-existing condition or was planned prior to the start of the study, the condition that led to the hospitalization should be recorded in the eCRF Medical History form. If the hospitalization arises from a pre-existing condition that did not worsen and the hospitalization was planned after the start of the study, the condition that led to hospitalization should be recorded in the AE page of the eCRF. In both cases, the condition that led to hospitalization should be recorded, and the relationship to study drug will be recorded as "Unrelated."

16.1.4 ACTION TAKEN AND OUTCOME

The Action Taken with NOX66 and doxorubicin for every AE will be reported as either "Dose Not Changed", "Dose Reduced", "Dose Withdrawn" or "Dose Delayed". The Outcome of each AE will be entered as either: Resolved, Resolved with Sequelae, Ongoing, Death, or Unknown as noted in Table 6.

Table 6 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.

16.2 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 stabilization (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.

16.2.1 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 dies or is lost to follow-up.

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

The detailed SAE reporting process will be provided to the sites.

16.2.2 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.

The Sponsor should be notified if the Investigator becomes aware of the development of a new primary cancer or of a congenital anomaly in a subsequently conceived offspring of a patient who participated in the study.

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

16.2.3 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, 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 IRB by a written safety report within 15 calendar days of notification.

17 CONDUCT OF STUDY

17.1 HUMAN RESEARCH

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (Committee for medicinal products for human use/ICH/135/95), and applicable regulatory requirements including the following:

- European Commission Directive (2001/20/EC Apr 2001)
- European Commission Directive (2005/28/EC Apr 2005)
- United States Food and Drug Administration GCP Regulations: CFR Title 21, parts 11, 50, 54, 56, and 312 as appropriate
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 November 2014 and/or
- Other applicable local regulations

The Protocol and all other relevant study documents (informed consent, advertising etc.) will be submitted to the appropriate IRB for approval. Written confirmation of approval (noting version/ date of all approved documents) must be received from the Investigator before the study commences and approval of all documents pertaining to this study will be kept in the Study Master File.

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

17.2 SUBJECT CONFIDENTIALITY

The Investigators and the Sponsor will preserve the confidentiality of all patients taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the patient's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, patients should be identified by a unique patient identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (e.g., signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the patient's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the patient that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the patient.

17.3 REGULATORY APPROVAL

The study protocol, patient information and consent form, the IB, any patient written instructions to be given to the patient, available safety information, patient recruitment

procedures (e.g., advertisements), information about payments and compensation available to the patients, and documentation evidencing the Investigator's qualifications should be submitted to the IRB for ethical review and approval according to local regulations, prior to the study initiation. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator and/or Sponsor must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation. If changes to the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to regulatory authorities and implementation of these changes happen only after approval by the relevant regulatory bodies, as required.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Regulatory Authority in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study patients against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the Investigator becomes aware of.

17.4 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 Conference on Harmonisation (ICH).

Compliance with these guidelines ensures compliance with the currently approved version of the Declaration of Helsinki (October 2000) with notes of Clarification in 2002 (Washington) and 2004 (Tokyo) and the Australian National Health and Medical Research Council Statement on Human Experimentation (2007) and any local legal and regulatory requirements.

The CRO monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of

clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each site. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to patient medical records and other study related records needed to verify the entries on the CRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study site may be selected for audit by representatives from the Sponsor. Audit of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

17.5 ADHERENCE TO PROTOCOL

No changes or deviations in the conduct of this protocol will be permitted, with the exception of emergency situations. If an emergency situation occurs 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 Investigators will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Sponsor, the Medical Monitor, and the IRB.

Notify the IRB 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.

17.5.1 PROTOCOL VIOLATION AND REPORTING

The Investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority, and which was given approval/favorable opinion by the IRB.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the patient. 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 SAEs according to the procedure described in Section 16.

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.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a patient was ineligible or received the incorrect dose or study treatment, and had at least one administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

17.6 SUPPLY OF NEW INFORMATION AFFECTING THE CONDUCT OF THE STUDY

When new information becomes available that may adversely affect the safety of patients or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, IRB, and regulatory authorities of such information, and when needed, will amend the protocol and/or patient information.

The Investigator should immediately inform the patient whenever new information becomes available that may be relevant to the patient's consent or may influence the patient's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the patient is willing to remain in the study.

If the patient information is revised, it must be re-approved by the IRB. The Investigator should obtain written informed consent to continue participation with the revised written information even if patients were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the patient should sign and date the revised ICF.

17.7 PROTOCOL AMENDMENTS

All changes to the protocol (modifications (e.g., changes to eligibility criteria, outcomes, analyses) must be documented by amendments, or administrative changes where applicable, and the amended protocol must be signed by Noxopharm and the Investigators. The amended protocol and a revised IC form, if necessary, will be submitted to each IRB for approval. If the protocol modifications affect the CRFs, they will also be revised and provided to the sites.

18 SUBJECT INFORMED CONSENT

The 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 patient's written consent. The patient and the person who conducted the informed consent discussion are to sign and personally date the consent form.

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, IRB 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.

19 DISCLOSURE OF DATA

19.1 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 eCRFs only by their patient number and initials.

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

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

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

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

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

19.1.1 STUDY RECORDS AND SOURCE DOCUMENTS

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

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

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

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

19.1.2 PRIOR TO STUDY COMMENCEMENT

Prior to the release of clinical study supplies and the study commences, the following documents must be provided:

i. An up-to-date, signed and dated Curriculum Vitae for all Investigators and relevant study staff.
ii. The signed Protocol and any Amendments.
iii. The signed clinical study agreement.
iv. The signed letter from the IRB giving approval for the study (version numbers/dates of all approved documents to be included), together with a letter of constitution of the IRB. Copies of any other correspondence with the IRB relevant to the study should also be supplied.
v. Current laboratory certification of the laboratories 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.

19.1.3 DOCUMENT RETENTION

The Investigator at each site will retain copies (electronic form that has been backed up to a server) 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.

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

The Sponsor will provide the 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 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.

19.1.4 ACCESS TO SOURCE DOCUMENTS

In order 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.

19.2 PUBLICATION POLICY

To avoid disclosures that could jeopardize proprietary rights, Investigators are required to submit all publications to the Sponsor prior to submission. The Sponsor will review any such submissions within 30 days of receipt. Therefore, the study site will have the opportunity to publish the results of the study, provided that Noxopharm has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of Noxopharm's Legal Department (intellectual property council) and with proper regard to the protection of patients' identities to a publisher.

The Sponsor must register the trial prior to commencement and communicate a summary of results on an approved registry (e.g. www.clinicaltrials.gov). Publication in medical or scientific journals should conform to guidelines set out in the International Committee of Medical Journal Editors (ICMJE)[1] and consult reporting standards such as the CONSORT[2] group and the individual journals. Available on http://www.icmje.org Available on http://www.consort-statement.org

20 ADDITIONAL SUBJECT CARE DURING POST-STUDY

20.1 EMERGENCY CONTACT

20.1.1 INVESTIGATOR

The 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 an intercurrent illness.

20.1.2 SPONSOR

In an emergency the Investigator should contact both the study sponsor and the Monitor by telephone.

20.2 LIABILITY AND INSURANCE

The Sponsor provides insurance for study patients to make available compensation in case of study-related injury.

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

With effect from the commencement of the study the sponsor will indemnify study participants.

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22 APPENDICES

22.1 CONSENT

A consent form and other related documentation will be provided to participants and authorized surrogates

22.2 SPECIMEN COLLECTION

22.2.1 CLINICAL LABORATORY TESTS

Urine pregnancy tests will be read at the site and will be obtained commercially. All clinical laboratory tests (serum chemistry, hematology and urinalysis, and cardiac biomarkers, BNP and troponin I) are to be done locally.

22.2.2 PHARMACOKINETIC, PHARMACODYNAMIC SAMPLES AND ELECTROCARDIOGRAPHIC TIMEPOINTS

22.2.2.1 Collection for Plasma Pharmacokinetic Samples

Blood samples for idronoxil and doxorubicin will be taken by venipuncture or cannula at time points detailed in Sections 11.4.3 and 22.2.2.2. Pre dose samples should be collected within 15 minutes prior to dosing. The sampling times for collection of blood for analysis of idronoxil, its metabolites, doxorubicin and doxorubicinol are listed in Table 7.

Table 7 Pharmacokinetic Sampling Times for NOX66 and Doxorubicin

Monotherapy and Cycle 1

Cycle / Day	D 1	D 2	D 7	Day 8	C1D2		C1D7	C1D8
Hours Post Dose	**Monotherapy [e]**				**NOX**	**Dox**	**NOX**	**NOX**
Pre-Dose	X	X	X		X[d]		X[g]	
0.5						X[f]		
1	X		X		X[e]			
2	X		X		X[e]			
3	X		X					
4	X		X		X[i]	X[f]		
6	X		X		X[i]	X[f]		
8	X		X	X[b]				X[b,e]
12				X[c]				X[c,e]

See footnotes on table below.

Cycles 2 to 6

Cycle	C2		C3				C4		C5				C6	
Day	D2		D2		D7	D8	D2		D2		D7	D8	D2	
Hours Post Dose	NOX	Dox	NOX	Dox	NOX	NOX	NOX	Dox	NOX	Dox	NOX	NOX	NOX	Dox
Pre-Dose	X[h]				X[g]		X[h]				X[g]		X[h]	
0.5		X[f]						X[fi]						X[f]
1														
2														
3														
4	X	X[f]	X				X	X[f]	X				X	X[f]
6														
8						X[b,e]						X[b,e]		
12						X[c,e]						X[c,e]		

Samples for idronoxil are to be collected in Potassium Oxalate/Sodium Fluoride containing tubes.

[b] Only for TID - 8 hours after the last dose of NOX66 on Day 7

[c] Only for BID - 12 hours after the last dose of NOX66 on Day 7

[d] Pre dose of NOX66

[e] Only for Dose Escalation Cohorts

[f] PK sample for Dox

[g] Prior to last morning dose of NOX66

[h] Prior to the morning dose of NOX66 administration (8or 12 hours after the last dose of NOX66 on Day 1).

[l] Only for Dose Expansion Cohort

The following PK samples can be obtained at the patient's home if needed: 1) 24-hour sample on Day 1 of Monotherapy period, 2) Day 1 of the Washout Period (8 or 12 hours after the last dose, of a TID or BID , dosing regimen, respectively) on Day 7 of Monotherapy period], 3) pre-dose Day 7 and at 8 or 12 hours after the last dose on Day 7 of a TID or BID , dosing regimen, respectively for Cycles 1, 3 and 5.

Blood samples for idronoxil and metabolites will be collected in 4 mL Vacutainer tubes containing Potassium Oxalate/Sodium Fluoride as anticoagulant for the preparation of plasma. Blood samples for doxorubicin and doxorubicinol will also be collected at specified timepoints in pre-chilled 4 mL Vacutainer tubes containing K_2EDTA as anticoagulant for the preparation of plasma. The details on sample processing will be available in the Laboratory Manual.

22.2.2.2 Shipping Plasma Pharmacokinetic Samples

For each cohort, plasma samples will be shipped directly to a nominated laboratory for bioanalytical sample analysis. Samples will be packed in sufficient dry ice to last 3 days and

prior-shipping notice should be sent to the bioanalytical laboratory. Details on sample packing and shipment will be provided in the Laboratory Manual.

22.2.2.3 ECG Times

The timepoints for ECG recordings prior to and after administration of idronoxil alone an in combination with doxorubicin are listed in Table 8 ECG Timepoints

Table 8 ECG Timepoints

Timepoint / Method	**Monotherapy Day 1**	**Monotherapy Day 7**		**C1 Day 2**		**C2-C6 Day 2**
	12-lead ECG	12-lead ECG	Holter	12-lead ECG	Holter	12-lead ECG
Pre-Dose (-0.75, -0.5 and -0.25 hrs prior to NOX66)	X	X		X		
Pre-Dose (-0.25 hrs prior to NOX66)						X
1 hr post NOX66 dose	X	X		X		X
2 hrs post NOX66 dose	X	X		X		X
5 hrs post NOX66 dose	X	X		X		X
8 hrs post NOX66 dose	X	X	X	X	X	X
12 hrs post NOX66 dose			X		X	
24 hrs post NOX66 dose			X		X	

The following windows are acceptable for performing the ECGs:

- +/-5 minutes for pre-dose ECGs required at -0.75, -0.5 and -0.25 hours prior to NOX66 administration.
- +/-10 minutes for post-dose ECGs required at 1 hour and 2 hours after NOX66 administration.
- +/-15 minutes for post-dose ECGs required at 5 hrs and 8 hours after NOX66 administration.

22.2.3 GENETIC MUTATIONS AND HISTOPATHOLGY

Blood samples for genetic mutations will be collected prior to the first dose of NOX66 and on Day 21, Cycle 6 (or Early Termination) for both parts.

Archival tissue sample if available (10 unstained histology slides) will be collected at Screening or at any time throughout the study (optional).

22.2.4 CHEMOKINES, CYTOKINES AND ENOX2

The laboratory that will assay the plasma samples for chemokines, cytokines and ENOX2 must use validated methods. The sampling times for collection of blood for pharmacodynamic variables are provided listed in Table 9.

Table 9 Pharmacodynamic Sampling time Points

Assay	**Blood Volume (mL)**	**Screening**[a]	**Day 7 Monotherapy**	**C3D1**	**C6D21/ET**[b]
			Dose Escalation		
Chemokines and cytokines	1 X 4	X	X	X	X
Immuno assays and lipidomic assays	4 X 4	X	X	X	X
Genetic mutation	2 x 4	X	NA	NA	X
			Dose Expansion		
Chemokines and cytokines	1 X 4	X	NA	X	X
Immuno assays and lipidomic assays	4 X 4	x		X	X
Genetic mutation	2 x 4	X		NA	X

[a]Pharmacodynamic samples should be collected only after eligibility confirmation at Screening, or otherwise can be collected at Monotherapy Day 1/Cycle 1 Day 1 prior to the first NOX66 administration.

[b] PD samples to be collected at Early Termination if the subject discontinues treatment prior to Cycle 6.

NA= not applicable; ET = Early Termination

The details on pharmacodynamic sample processing and shipping requirements will be provided in the Laboratory Manual.

22.3 INHIBITORS AND INDUCERS OF CYTOCHROME P450 ENZYMES

A list of medications that can inhibit or induce cytochrome P450 enzymes are shown in

Table 10 Inhibitors and Inducers of Cytochrome P450 Enzymes

INHIBITORS

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's response to that particular medication, e.g. making it ineffective.

- A Strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A Moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- A Weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
fluvoxamine	clopidogrel	gemfibrozil[2]	fluconazole[2]	PPIs:	bupropion	diethyl-dithiocarbamate[2]	HIV Antivirals:
ciprofloxacin	thiotepa			esomeprazole	cinacalcet		indinavir
	ticlopidine[2]	trimethoprim	amiodarone	lansoprazole	fluoxetine	disulfiram	nelfinavir
cimetidine				omeprazole	paroxetine		ritonavir
	voriconazole		efavirenz	pantoprazole	quinidine[1]		
amiodarone		glitazones	fenofibrate				clarithromycin
efavirenz		montelukast[1]	fluconazole		duloxetine		itraconazole[1]
fluoroquinolones		quercetin[1]	fluvastatin		sertraline		ketoconazole
fluvoxamine			fluvoxamine[2]	Other:	terbinafine		nefazodone
furafylline[1]			isoniazid	chloramphenicol			saquinavir
interferon			lovastatin	cimetidine	amiodarone		
methoxsalen			metronidazole	felbamate	cimetidine		telithromycin
mibefradil			paroxetine	fluoxetine			
ticlopidine			phenylbutazone	fluvoxamine	celecoxib		aprepitant
			probenicid	indomethacin	chlorpheniramine		erythromycin
			sertraline	isoniazid	chlorpromazine		fluconazole
			sulfamethoxazole	ketoconazole	citalopram		grapefruit juice
			sulfaphenazole[1]	modafinil	clemastine		verapamil[2]
			teniposide	oral contraceptives	clomipramine		diltiazem
			voriconazole	oxcarbazepine	cocaine		cimetidine
			zafirlukast	probenicid	diphenhydramine		amiodarone
				ticlopidine	doxepin		NOT azithromycin
					doxorubicin		
					escitalopram		

topiramate
voriconazole

halofantrine
haloperidol
histamine H1 receptor antagonists
hydroxyzine
levomepromazine
methadone
metoclopramide
mibefradil
midodrine
moclobemide
perphenazine
promethazine
ranitidine
reduced-haloperidol
ritonavir
ticlopidine
tripelennamine

chloramphenicol
boceprevir
ciprofloxacin
delaviridine
diethyl-dithiocarbamate
fluvoxamine
gestodene
imatinib
mibefradil
mifepristone
norfloxacin
norfluoxetine
starfruit
telaprevir
voriconazole

INDUCERS

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
broccoli	artemisinin	rifampin[1]	carbamazepine	carbamazepine	dexamethasone	ethanol	HIV Antivirals:
brussel sprouts	carbamazepine		enzalutamide	efavirenz	rifampin	isoniazid	efavirenz
carbamazepine	efavirenz			enzalutamide			nevirapine
char-grilled meat	nevirapine		nevirapine				
insulin	phenobarbital		phenobarbital	norethindrone			barbiturates
methylcholanthrene[1]	phenytoin		rifampin	NOT pentobarbital			carbamazepine
modafinil	rifampin		secobarbital	prednisone			
nafcillin			St. John's Wort	rifampicin[1]			enzalutamide
beta-naphthoflavone[1]				ritonavir			glucocorticoids
omeprazole[1]				St. John's Wort			modafinil
rifampin							oxcarbazepine
tobacco							phenobarbital[2]
							phenytoin[2]
							pioglitazone
							rifabutin
							rifampin[1]
							St. John's Wort
							troglitazone[1]