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NOX66-001A
Statistical Analysis Plan

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NOXOPHARM LIMITED

Statistical Analysis Plan

Written by Datapharm Australia Pty. Ltd.

Prepared for

NOXOPHARM LIMITED

Protocol Number: NOX66-001A

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

SAP Version: Final 1

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Statistical Analysis Plan Approval Page

Study Title:	Phase Ia/Ib and Potential Phase IIa Study of the Safety and Pharmacokinetics of NOX66 Both as a Monotherapy and in Combination with Carboplatin in Patients with Refractory Solid Tumours
Protocol Number:	NOX66-001A (Version 3.0, 30 June 2017)

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The undersigned have reviewed this document and agree with the analysis to be performed on the data originating from the study protocol identified above.

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1. ABBREVIATIONS

Abbreviation/term	Definition
AUC	Area under the curve
C_{max}	Maximal concentration
CR	Complete recovery
DD	Drug Dictionary
DLT	Dose limiting toxicity
eCRF	Electronic case record form
MedDRA	Medical Dictionary for Regulatory Activities
NOX66	idronoxil
PR	Partial recovery
SD	Standard deviation
T_{max}	Time at which maximal concentration occurs
WHO	World Health Organization

2. INTRODUCTION, STUDY DESIGN AND OBJECTIVES

2.1 Introduction

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

The failure of chemotherapy and radiotherapy to have a bigger impact on survival prospects is due to 2 factors. First is their general poisoning effect which prevents them from being used at higher and more effective dosages. Second is the ability of cancer cells to become resistant to both drugs and radiation. The problem of resistance has been identified as the single largest problem facing better management of cancer. Without this resistance, cancer cells would be killed by much lower levels of chemotherapy or radiotherapy.

- The objective of the current global NOX66 program is to use its active drug, idronoxil (NOX66), to enhance the effects of standard chemotherapy and palliative radiotherapy so that in combination with: standard doses of chemotherapy in patients who have become resistant to treatment may provide a therapeutic response (reversal of resistance)
- standard doses of chemotherapy in patients naïve to treatment may increase the level of cell death (sensitization)
- low doses of chemotherapy in patients unable to tolerate full dose chemotherapy may provide a therapeutic benefit, whilst minimising adverse events
- palliative dose radiotherapy may provide a therapeutic benefit at the site(s) of irradiation (Direct response) and at sites distant from irradiation (abscopal effect)

2.2 Study design

This is a Phase I, open-label, non-randomised, dose-escalation (two-step) study of the experimental drug, NOX66, in a suppository dosage formulation (NOX66) in patients with refractory solid tumours that have stopped responding to standard treatment options. The patients will have solid cancers selected from 5 phenotypes: prostate, breast, ovarian, lung, head and neck.

The study has two confirmed arms: a Phase Ia (Run-In) Arm where NOX66 is used alone and a Phase Ib (Combination) Arm where NOX66is used in combination with carboplatin.

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

Sixteen (16) evaluable patients will be recruited and 8 patients allocated to each of two cohorts – Cohort 1 and Cohort 2. Cohort 1 will receive an NOX66 dosage of 400 mg daily; Cohort 2, 800 mg daily. Recruitment into Cohort 2 will not occur until at least 7/8 Cohort 1 patients have completed at least 1 Phase Ia Treatment Cycle without Dose-limiting Toxicity (DLT).

In the **Phase Ia (Run-In) Arm**, patients will self-administer NOX66 rectally either once or twice (12-hourly) daily for 14 consecutive days for one (21-day) Treatment Cycle.

The main purpose of the Phase Ia Arm is to confirm the tolerability of NOX66 formulation when used for 14 consecutive days in a 21-day monotherapy cycle..

The **Phase Ib (Combination) Arm** will commence immediately following the Phase Ia (Run-In) Arm and will comprise NOX66 being administered in combination with carboplatin. Patients will continue in the same cohorts and remain on the same NOX66 dosage.

Within each 28-day combination treatment cycle, NOX66 treatment will commence on Day 1 and continue daily for 7 consecutive days; carboplatin will be administered intravenously on Day 2.

There will be two different dosages of carboplatin administered: AUC = 4 (600 mg maximum) and AUC = 6 (900 mg maximum). Patients will start with the lower dose and receive that for 3 Treatment Cycles, then progress onto the higher dosage of carboplatin which they will receive for up to a further 3 Treatment Cycles.

The primary aim of this phase is to investigate if NOX66 can induce a meaningful clinical response (complete or partial remission by RECIST criteria) in combination with carboplatin in cancers that have stopped responding to standard chemotherapy and generally would be considered unlikely to respond to further standard therapy. Furthermore, it will be investigated if a meaningful anti-cancer effect is possible combined with a dosage of carboplatin that would otherwise be regarded generally as well tolerated but unlikely to deliver a significant anti-cancer effect.

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

2.3 Study objectives

The primary objectives of this study are:

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

The secondary objectives are:

- to characterise some key pharmacokinetic features of NOX66 when administered rectally
- to determine if various biomarkers of NOX66 biologic activity have any correlation to the efficacy or toxicity of NOX66 in combination with carboplatin.

3. ANALYSIS POPULATIONS AND GENERAL STATISTICAL METHODOLOGY

This analysis plan is based on protocol version 3.0, dated 30 June 2017.

3.1 Analysis populations

There will be three study populations defined for this study.

The safety population will consist of all patients who received at least one dose of NOX66. This population will be used in all safety summaries.

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

The pharmacokinetic/biomarker population will be a subset of the safety and efficacy populations and consist of all patients who have sufficient NOX66 plasma data or biomarker plasma data for analysis. All such patients will be evaluated unless significant protocol deviations have impacted the data. Changes to the procedures, which may impact the quality of pharmacokinetic data, will be considered significant protocol deviations. Examples include sample processing errors that lead to inaccurate bio-analytical results and/or inaccurate dosing on the day of pharmacokinetic sampling.

3.2 Visit windows

The Screening visit must be at least 7 days prior to the first dose of NOX66.

All other visits should be within ±1 day of the planned study visit. All visits will be analysed based on the planned visit, as opposed to when the visit actually occurred.

3.3 General statistical methodology

Patients will be analysed by both study arm and dose cohort. Patients will be assigned sequentially to the two cohorts of 400 mg NOX66 (1 suppository per day) or 800 mg NOX66 (2 suppositories per day). Each cohort will be identified by '400 mg' or '800 mg'. The first 16 patients recruited to the study will be included in the study arm identified as 'Phase I' that will consist of a 21-day monotherapy phase and combination phase of up to 6 x 28-day cycles. Additional replaced patients will be included in the combination phase of up to 6 x 28-day cycles with the highest tolerated NOX66 dose cohort.

Descriptive statistics or continuous measures will include number of observations (n), mean, standard deviations (SD), minimum, median and maximum. For categorical measures, the descriptive statistics will include count and percent of the cohort.

There are four investigative sites in this study. There will be no analysis by study site.

The Medical Dictionary for Regulatory Affairs (MedDRA) will be used to code both medical history events and adverse events recorded during the study. The latest available version of MedDRA will be used to perform the coding at the end of the study. The World Health Organization (WHO) Drug Dictionary (DD) will be used to code concomitant medications taken prior to and during the study treatment period. The latest available version of WHO DD will be used to perform the coding at the end of the study.

As this is a dose escalation study, an 'Overall' column will be calculated for all tables.

All programming will be done in SAS version 9.4.

Missing data will remain missing with the exception that, for safety data, if there are corresponding unscheduled visits where data values exist, and those data are missing for the prior, scheduled, visit, then the values from the unscheduled visit will be imputed.

3.4 Data handling

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

The Principal Investigator will be responsible for the timeliness, completeness, and accuracy of the information entered on the CRF. The Principal Investigator will

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

4. SUBJECT DISPOSITION AND WITHDRAWAL

4.1 Subject disposition

Subject disposition for each phase and cohort will be presented as both flow chart and table. Each will show: the number of subjects enrolled, and the number of cycles completed in each phase.

4.2 Study completion and withdrawal

A table will present the number and percentage of patients who complete each phase of the study by cohort and where premature withdrawals occur, the reason for each withdrawal.

5. DEMOGRAPHIC AND OTHER CHARACTERISTICS AT BASELINE

5.1 Demographic data

Demographic data collected Screening and the Cycle 1A Day 1 (baseline) visits, including age, gender, height, weight, BMI and race together with other characteristics recorded in the CRF will be summarised by descriptive statistics or frequency tabulations by cohort. If Phase II of the Study is executed, their demographic data will be summarised and presented separately. An ‘Overall’ column will be presented.

5.2 Disease history

Characteristics of disease history will be summarised and tabulated by cohort and overall within each phase of study. An ‘Overall’ column will be included in the table.

5.3 Medical history

Medical history events will be coded by using the latest available version of MedDRA. Prior and current events will be summarised and tabulated separately by System Organ Class and Preferred term and cohort. An ‘Overall’ column will be included in the table.

5.4 Prior medications

Prior medications will those medications taken and ceased prior to the first dose of study drug. Prior medications will be coded by using the latest available version of the WHO DD. Prior medications will be summarised by Levels 1 and 2 codes and terms and by cohort, with an 'Overall' column.

5.5 Concomitant medications

Concomitant medications will be those medications taken during the study treatment period. Concomitant medications will be coded by using the latest available version of the WHO DD. Concomitant medications will be summarised by Levels 1 and 2 codes and terms and by cohort, with an 'Overall' column. New medications will be defined as those drugs commenced after the first dose of the study treatment. New medications will be summarised by Levels 1 and 2 codes and terms and by cohort, with an 'Overall' column.

5.6 Prior treatments

Chemotherapy and other anti-cancer treatments received by patients prior to commencement of this study will be summarised and tabulated by cohort, with an 'Overall' column.

5.7 ECOG status

ECOG status measured at Screening will be summarised and tabulated by cohort, with an 'Overall' column.

6. COMPLIANCE

Compliance will be calculated as the percentage of drug to be given versus what is actually received by each patient within each phase of the study. Compliance will be summarised and tabulated for each cohort with an 'Overall' column.

7. EFFICACY ANALYSES

There are no statistically powered efficacy objectives in this study, however, tumour measurements, RECIST criteria response, progression-free and overall survival will be analysed for signals of treatment efficacy.

7.1 Efficacy

Tumour measurements will be assessed by radiological methods. Longest dimensions for each target lesion within each patient will be summed at each measurement time. Sums will be analysed by descriptive statistics by cohort for each measurement time within each phase of the study.

Response to treatment, as measured by the RECIST criteria, as well as duration of response will be assessed following each radiological assessment. The best overall response and the duration of that response will be summarised and tabulated by cohort. Duration of the objective response will be defined as the time from the initial CR or PR to the time of disease progression or death on study, whichever occurs first.

For patients who are alive and have not experienced disease progression on study, duration of objective response will be censored at the day of the last tumour assessment. Time to disease progression is defined as the time from the first day of study drug administration (Day 1) to disease recurrence or progression on study. Progression free survival (PFS) is defined as the time from the first day of study drug administration (Day 1) to disease recurrence or progression, or death on study. Patients who are alive and disease progression-free will be censored at the date of last disease evaluation. Progression-free survival and overall survival will be analysed using the Kaplan-Meier actuarial method. Median times and 95% confidence intervals will be computed by cohort.

7.2 Pharmacokinetics

Plasma and 24-hour urine levels of NOX66 and NOX66 metabolites (idronoxil glucuronide, idronoxil sulphate) will be measured. Pharmacokinetic parameters will minimally include C_{max}, T_{max}, $AUC_{0\text{-}24h}$r, $AUC_{0\text{-}\infty}$, and $t_{1/2}$ and be calculated using standard analysis. Descriptive results will be presented for the pharmacokinetic parameters by dose cohort.

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

7.3 Exploratory analysis

Exploratory analyses will be performed to determine if any relationships exist between disease status at study entry, prior treatments (chemotherapy and other cancer treatments), tumour genetic markers or biomarkers and efficacy outcomes for patients.

8. SAFETY ANALYSES

8.1 Exposure to study treatments

Exposure to study treatments will be calculated as date of last treatment minus date of start of treatment + 1. If unknown, the date of last treatment will be estimated using the last visit date minus 1 and imputed.

8.2 Adverse events

Adverse events will be coded by MedDRA SOC and Preferred Term, summarised and tabulated for the safety population in the monotherapy arm (phase 1a), in combination arm (phase 1b) with low dose (AUC4) carboplatin and with high dose (AUC6) carboplatin and overall treatment. For each preferred term the number and percent of subjects reporting each adverse event will be tabulated by cohort and 'Overall'. These include:

- Adverse event summary table
- Adverse events occurring prior to study commencement
- All adverse events occurring after study commencement
- Most common (>15 %) treatment-emergent adverse events in any cohort
- Treatment emergent adverse events that were possibly, likely or certainly related to the study medication
- Serious adverse events
- Severe adverse events
- Adverse events causing withdrawal
- All adverse events by maximum severity and relationship to study treatment, with subject identification.

8.3 Serious adverse events

Serious adverse events will be tabulated in the same way as all adverse events. In addition, anecdotal descriptions of each serious adverse event will be provided.

8.4 Vital signs

Vital sign variables, including standing and supine systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature with change from Baseline will be summarised and tabulated by cohort and study visit (cycle and cycle day) by cohort.

8.5 Laboratory safety measurements

Serum biochemistry values, with change from Baseline and the number of clinically significant results will be summarised by cycle, cycle day and cohort. If multiple units are detected for any parameters, conversion of appropriate records to a common unit will be completed prior to summary and tabulation.

Haematology values, with change from Baseline and the number of clinically significant results will be summarised by cycle, cycle day and cohort. If multiple units are detected for any parameters, conversion of appropriate records to a common unit will be completed prior to summary and tabulation.

Urinalysis results for categorical measures will be summarised and tabulated, with change from Baseline (worsened, no change or improved) by cycle, cycle day and cohort. Continuous measures, pH and specific gravity, will be summarised and tabulated separately in a similar manner.

Urine microscopy results will be summarised and tabulated by cycle, cycle day and cohort.

8.6 Other safety analyses

Physical examination results will be summarised and tabulated by body system, cycle and cycle day and cohort, with change from Baseline (Abnormal to normal, Normal to abnormal).

ECG parameters will be summarised and tabulated by cycle, cycle day and cohort. ECG findings will summarised and tabulated separately by cycle, cycle day and cohort.

Biomarker values will be summarised and tabulated, with change from Baseline by cycle, cycle day and cohort for available data, dependent on the development of the specific biomarker assay.

9. INTERIM ANALYSES

Not applicable.

Data will be reviewed periodically to determine that DLTs are not occurring and to approve recruitment into later phases of the study.

10. CHANGES FROM THE PROTOCOL

All changes in procedures from the protocol will be documented in the final clinical study report.

11. TABLE AND FIGURE LISTINGS

Table Section	Table Title (Population)
Section 10.1	Patient disposition (All populations)
	Completion and withdrawal (Safety population)
Section 11.2	Demographics (Safety population)
	Disease history (Safety population)
	Prior medical history events (Safety population)
	Current medical history events (Safety population)
	Prior medications (Safety population)
	Concomitant medications (Safety population)
	New medications (Safety population)
	Prior chemotherapy (Safety population)
	ECOG status (Safety population)
Section 11.3	Compliance (Safety population)
Section 11.4	Tumour measurements (Efficacy population)
	RECIST response rates and durations (Efficacy population)
	Progression-free survival (Efficacy population)
	Overall survival (Efficacy population)
	Plasma concentrations (PK population)
	Pharmacokinetic coefficients (PK population)
Section 12.1	Exposure (Safety population)
Section 12.2	Summary of adverse events (Safety population)
	Pre-treatment adverse events (Safety population)
	Treatment emergent adverse events (Safety population)
	Treatment emergent adverse events considered possibly, probably or definitely related to study treatment (Safety population)
	Severe adverse events (Safety population)
	Adverse events resulting in withdrawal (Safety population)
Section 12.3	Deaths and serious adverse events
Section 12.4	Serum biochemistry (Safety population)
	Biochemistry shift table (Safety population)
	Haematology (Safety population)
	Haematology shift table (Safety population)
	Categorical urinalysis results (Safety population)

	Urinary pH and specific gravity (Safety population)
	Urinary microscopy (Safety population)
Section 12.5	Vital signs (Safety population)
	Physical examination (Safety population)
	ECG parameters (Safety population)
	ECG findings (Safety population)
	Biomarkers (Safety population)

Figure Section	**Figure Title (Population)**
Section 11.4	Tumour measurements (Efficacy population)
	Pattern of response by cohort (Efficacy population)
	Progression-free survival (Efficacy population)
	Overall survival (Efficacy population)
	Plasma concentrations by cohort (PK population)
Section 12.2	Most common preferred terms (Safety population)
Section 12.5	Biomarkers (for each parameter) (Safety population)