PledPharma

POLAR

STATISTICAL ANALYSIS PLAN

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Date	2 September 2020
Version	1.0

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SIGNATURE PAGE

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1. INTRODUCTION

The pivotal Phase 3 POLAR program, studying calmangafodipir for the prevention of chemotherapy induced peripheral neuropathy, consists of two studies: POLAR-A and POLAR-M.

- POLAR-A is a placebo controlled, randomised (1:1) Phase III study of calmangafodipir 5 µmol/kg in combination with mFOLFOX6 compared to placebo+mFOLFOX6 in patients with adjuvant treatment of stage III or high-risk stage II colorectal cancer.
- POLAR-M is a placebo controlled, randomised (1:1:1) Phase III study of calmangafodipir in two different doses, 2 µmol/kg and 5 µmol/kg in combination with mFOLFOX6 compared to placebo+mFOLFOX6 in patients with metastatic CRC.

Patient recruitment in the POLAR-A and POLAR-M studies was initiated in late 2018 with the first patient randomised in on January 15, 2019, in POLAR-A and on POLAR-M on January 21, 2019.

On January 23, 2020, the Sponsor announced that the US Food and Drug Administration (FDA) had issued a clinical hold in the US of the POLAR program. The implication was that recruitment and dosing of patients in the POLAR-M study was halted in the US. Based on the evaluation of the independent Drug Safety Monitoring Board (DSMB), the Sponsor's position was that the overall safety profile for PledOx supported the continuation of the POLAR program and both studies continued as planned in Europe and Asia with dosing and further recruitment.

On March 1, 2020, the Sponsor decided to place recruitment and dosing of patients in the POLAR program on hold. The decision followed interactions with the French regulatory authority, ANSM, and the clinical hold issued by the US Food and Drug Administration (FDA) earlier in the year and was due to 4 observed events related to seizure. The Sponsor maintained its position that these events are not related to calmangafodipir, a position which was also supported by the DSMB and an additional independent external evaluation of these cases.

On April 6, 2020, the Sponsor decided to close the POLAR program early with a data cut-off targeted for the third quarter 2020 (further detailed later in this document). The decision was taken after a recommendation from the DSMB to stop the studies due to an accumulation of severe allergic reactions, primarily observed after repeated dosing.

Based on the development of the POLAR studies, a re-assessment of the sample size assumptions is needed to determine a reasonable statistical approach to the analysis of the POLAR studies.

The POLAR studies were designed based on the following sample size assumptions:

- POLAR-A: With 112 patients per group, the POLAR-A study has 91% power to detect a reduction (improvement) from 40% to 20% (OR = 0.375) in the primary endpoint using two-sided test controlled at the 0.05 type-I error rate. To account for 20% dropout in the study, in total 280 patients (140 patients per arm) will be randomised.
- POLAR-M: With 112 patients per group, the POLAR-M study has 91% power to detect a reduction (improvement) from 40% to 20% (odds ratio = 0.375) in the primary endpoint using two-sided test controlled at the 0.05 type-I error rate. To account for 20% dropout in the study, in total 420 patients (140 patients per arm) will be randomised.

Table 1: Patient disposition in the POLAR studies

	POLAR-A	POLAR-M	Total
Number of patients randomised	301	290	591
Number of patients dosed with ≥1 cycle of IMP	297	285	582
Number of patients dosed with ≥6 cycles of IMP	257	194	451
Number of patients dosed with ≥12 cycles of IMP	107	98	205

A total of 591 patients was randomised in the POLAR program and 582 patients dosed, of which 451 patients completed 6 cycles and 205 patients completed 12 cycles (see Table 1).

There are two main contributing factors to take into account when designing a reasonable statistical approach to the analysis of the POLAR studies:

1) POLAR-M only randomised 290 out of the planned 420 patients. This, together with the reduced dosing of patients (see bullet 2 below) means a separate primary analysis based on this data set cannot be supported.
2) Due to the Sponsor's decision to place the dosing of patients on hold on March 1, 2020, not all patients have had sufficient dosing of IMP to expect the full treatment effect of active treatment as assumed in the sample size calculation.

Taking these two aspects into consideration account (the fewer number of randomised patients and the reduced dosing of patients) a reasonable statistical approach is to conduct a combined primary analysis across the two studies, with the data from the two studies regarded as strata, based on a modified ITT analysis set defined by the eligibility of dosing with IMP as intended in the clinical study protocol. In addition, a standalone analysis of the primary endpoint in the fully recruited POLAR-A study will be conducted if the combined analysis is statistically significant. This approach will be further detailed in this document.

All analyses will be provided using the combined data from the two studies. However, both POLAR studies will also be analysed and reported separately.

This SAP is based on protocol versions 7.0/8.0 dated 09JAN2020/17APR2020 and will cover both POLAR-A, POLAR-M and the combined analyses across studies. The SAP will be reviewed at the blind review of the data before database lock and will be finalised before breaking the blind and database lock.

The table, listing and figure shells will be supplied in a separate document "POLAR – Statistical Output Specification".

The analysis and statistics reporting will be conducted at Binomial Sweden AB using SAS version 9.4.

2. STUDY OBJECTIVES AND DESIGN

2.1 POLAR-A

2.1.1 Primary Objective

The primary objective of the study is to compare PledOx (5 µmol/kg) vs placebo with respect to the proportion of patients with moderate or severe chronic CIPN.

2.1.2 Secondary Objectives

The secondary objectives of the study are to compare PledOx vs placebo regarding the following:

Efficacy

- The proportion of patients with mild, moderate or severe chronic CIPN
- The sensitivity to touching cold items
- The cumulative dose of oxaliplatin during chemotherapy
- The vibration sensitivity on the lateral malleolus
- The worst pain in hands or feet
- The functional impairment (in the non-dominant hand)
- The sustained efficacy on prevention of CIPN during long-term follow-up

Safety

- DFS
- Safety and tolerability

2.1.3 Exploratory Objectives

The exploratory objectives of the study are to compare PledOx vs placebo regarding the following:

- Chronic CIPN by supporting analysis using the full Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity-13-item subscale (FACT/GOG-NTX-13)
- The cumulative dose of 5-FU during chemotherapy
- For both oxaliplatin and 5-FU: Dose intensity, number of cycles, dose reductions, reason(s) for dose reductions, patients with dose delays, and length of dose delays
- The functional impairment (in the non-dominant hand) during long-term follow-up.
- The worst pain in hands or feet during long-term follow-up
- QoL/health status
- Health economic impact

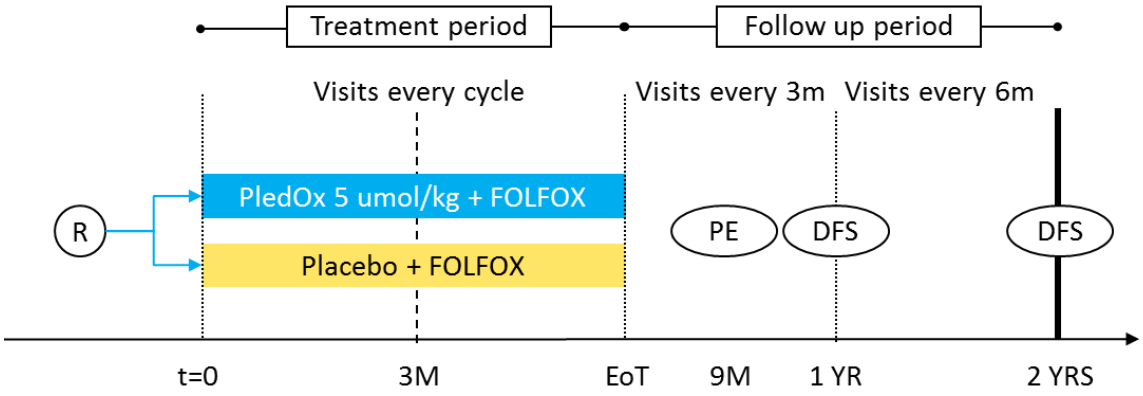
2.1.4 Study Design

POLAR-A is a Phase 3, multicenter, double-blind, placebo-controlled study using PledOx for prevention of chronic CIPN induced by oxaliplatin in patients with pathologically confirmed CRC, who are indicated for adjuvant mFOLFOX6 chemotherapy for up to 6 months.

Patients will be randomised in a 1:1 ratio to 1 of 2 treatment arms:

- Arm A: PledOx (5 µmol/kg) + mFOLFOX6 chemotherapy
- Arm B: Placebo + mFOLFOX6 chemotherapy

Figure 1 Polar-A Study Design



t=0 (baseline: Day 1, Cycle 1); R=randomization; EoT=end of treatment; DFS=disease free survival

Note: CIPN will be evaluated by the first 4 items of the FACT/GOG-NTX-13 (i.e. FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet, also at 9, 12, 18 and 24 months after the first dose of IMP

2.2 POLAR-M

2.2.1 Primary Objective

The primary objective of the study is to compare each dose of PledOx (2 and 5 µmol/kg) vs placebo with respect to the proportion of patients with moderate or severe chronic CIPN.

2.2.2 Secondary Objectives

The secondary objectives of the study are to compare each dose of PledOx vs placebo regarding the following:

<u>Efficacy</u>

- The proportion of patients with mild, moderate or severe chronic CIPN
- The sensitivity to touching cold items
- The cumulative dose of oxaliplatin during chemotherapy
- The vibration sensitivity on the lateral malleolus
- The worst pain in hands or feet
- The functional impairment (in the non-dominant hand)
- The sustained efficacy on prevention of CIPN during long-term follow-up

<u>Safety</u>

- Overall response rate (ORR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety and tolerability

2.2.3 Exploratory Objectives

The exploratory objectives of the study are to compare each dose of PledOx vs placebo regarding the following:

- Chronic CIPN by supporting analysis using the full FACT/GOG-NTX-13
- The cumulative dose of 5-FU during chemotherapy

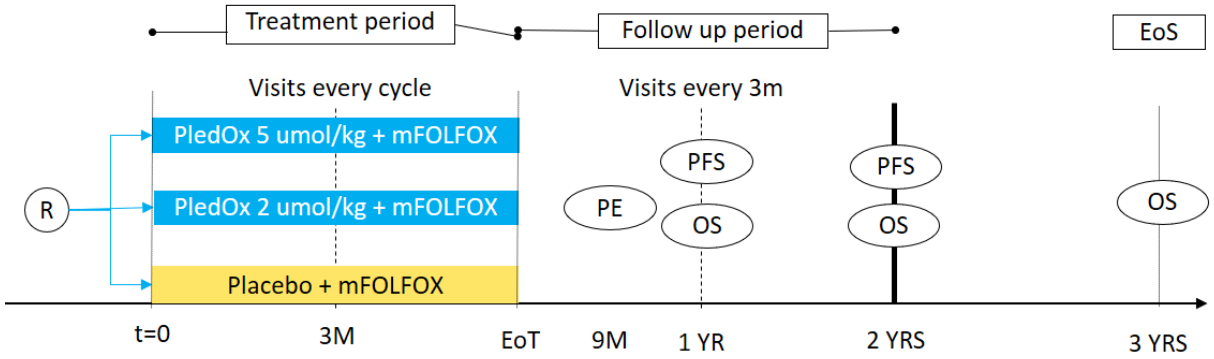
- For both oxaliplatin and 5-FU: Dose intensity, number of cycles, dose reductions, reason(s) for dose reductions, patients with dose delays, and length of dose delays
- The pharmacokinetic (PK) profile of PledOx with multiple dosing (only at pre-selected sites and in 84 patients in total)
- The QT/QTc interval using a 12-lead electrocardiogram (ECG) only at pre-selected sites and in 84 patients in total)
- The functional impairment (in the non-dominant hand) during long-term follow-up
- The worst pain in hands or feet during long-term follow-up
- QoL/health status
- Health economic impact

2.2.4 Study Design

POLAR-M is a Phase 3, multicenter, double-blind, placebo-controlled study to establish the efficacious dose of PledOx in prevention of chronic CIPN induced by oxaliplatin. Patients with metastatic CRC, who are indicated for first-line modified FOLFOX-6 (mFOLFOX6) chemotherapy for at least 3 months, without any pre-planned treatment breaks, will be randomised in a 1:1:1 ratio, stratified by region (Asia, non-Asia) and PK sub-study (yes, no), to one of three treatment arms:

- Arm A: PledOx (2 µmol/kg) + mFOLFOX6 chemotherapy
- Arm B: PledOx (5 µmol/kg) + mFOLFOX6 chemotherapy
- Arm C: Placebo + mFOLFOX6 chemotherapy

Figure 2. POLAR-M Study Design



t=0 (baseline: Day 1, Cycle 1); R=randomization; EoT=end of treatment; PFS=progression-free survival; OS=overall survival; EoS=end of study

Note: CIPN will be evaluated by the first 4 items of the FACT/GOG-NTX-13 (i.e. FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet, also at 12, 15, 18, 21 and 24 months after the first dose of IMP

2.3 Visit Structure

The visit structure and scheduled assessments are detailed in Section 5.2 and Appendix 1 in the study protocols.

2.4 Sample Size

As stated in Introduction the dosing of IMP stopped earlier than planned. Hence, the sample size assumptions originally stated in the protocols do not longer hold. In POLAR-A a total of n=301 patients have been randomised as compared to the planned n=280, and in POLAR-M n=290 patients have been randomised as compared to the planned n=420. The sample size protocol text below are stated for reference.

Protocol text (Section 10.2 in the CSPs)

The assumption of the proportion of patients who will satisfy the criteria for the primary endpoint in the untreated (placebo) study population is based on the results in the SCOT trial. Results were presented at ASCO 2017 and roughly 40% of the placebo population had symptoms graded "quite a bit/very much", which corresponds to 3 or more in this study.

With 112 patients per group, the **POLAR-A** study has 91% power to detect a reduction (improvement) from 40% to 20% (OR = 0.375) in the primary endpoint using two-sided test controlled at the 0.05 type-I error rate. To account for 20% dropout in the study, in total 280 patients (140 patients per arm) will be randomised.

With 112 patients per group, the **POLAR-M** study has 91% power to detect a reduction (improvement) from 40% to 20% (odds ratio = 0.375) in the primary endpoint using two-sided test controlled at the 0.05 type-I error rate. To account for 20% dropout in the study, in total 420 patients (140 patients per arm) will be randomised.

Sample size assumptions will be monitored in a blinded fashion as part of the regular monitoring of the study. In case there are indications these are not met; a re-estimation of the sample size may occur.

2.5 Changes From the Protocol Planned Analysis

Premature stop of administration of IMP in both POLAR-A and POLAR-M as well as the premature stop of recruitment in POLAR-M has several implications for the statistical analyses and the evaluation of the study data:

- Primary analysis. The Cochran-Mantel-Haenszel method described in the protocols has been fully specified to also include adjustment for cumulative oxaliplatin exposure. This amounts to replacing N, the number of subjects, in the divisor of the event rate calculation with cumulative oxaliplatin exposure. Also, in the protocols the CMH approach also adjust for FACT/GOG at baseline, but since there were very few patients with CIPN at baseline the primary analysis described in Section 5.1.1. does not include FACT/GOG at baseline.
- A negative binomial model will also be applied to the primary endpoint data as a supportive or exploratory analysis.
- Earlier stop of recruitment in POLAR-M has resulted in actual n=290 randomised patients as compared to the planned n=420.
- The primary analysis will be on the combined dataset including both POLAR-A and POLAR-M where study will be used as a stratification factor in all statistical analyses. Both studies will also be reported separately (see details in Section 3).
- Due to the lack of exposure of IMP a modified ITT (mITT) analysis set has been defined that will replace the Full Analysis Set (FAS). See further details in Section 3.1.
- Statistical analyses and summary tables will include data up to 12 months after the first dose of IMP (Assessment Visit 4). Data that has been collected after Assessment Visit 4 will only be included in the listings by patient.

Miscellaneous changes from the protocol planned analyses:

- The endpoint "mean health index using the FACT/GOG" as stated in the protocols will not be analysed.
- The variable Body Temperature although specified in vital signs section of the protocol has not been collected in the studies.
- In the CSP it says "PledOx Toxicities" but has been re-defined here in the SAP as "IMP Toxicities" since that is the way the data is collected and reported.

3. GENERAL STATISTICAL PRINCIPLES

Testing Procedure. The formal testing procedure of the primary endpoint is first to perform the analysis on PledOx 5 µmol/kg vs Placebo on both POLAR-A and POLAR-M studies combined. If the results are statistically significant then the same analysis will be performed on the POLAR-A study alone. All tests will be done on the 0.05 level of significance.

Statistical analyses will include stratification factors for study (POLAR-A / POLAR-M) and region (Asia/non-Asia).

3.1 Analysis Sets

The analysis set "All randomised patients (ITT)" consists of all patients who were assigned a randomisation number, irrespective of the treatment they received, if any.

The modified ITT (mITT) analysis set includes patients that fulfil at least one of the following criteria:

1. the patient was randomised prior to December 1, 2019 (ie the patient was eligible for at least 3 months of IMP) and had at least one post-baseline assessment for efficacy, or
2. the 3 month Assessment Visit occurred prior to 1 March, 2020, or
3. the patient received the 6th cycle of IMP after 1 March, 2020.

Patients will be analysed according to the treatment they are assigned to at randomisation, irrespective of what treatment they actually received.

The safety analysis set (SAF) consists of all randomised patients who receive at least one dose of IMP. Patients will be analysed according to the randomised study treatment actually received.

The list of patients to be included in each of the analysis sets is to be agreed between the project statistician and the Sponsor prior to unblinding, once all study data is available.

All enrolled patients will be listed indicating their membership to each analysis set along with the reason for exclusion.

The PK population (POLAR-M only) includes a subset of patients at pre-selected sites in all participating regions, where blood samples will be collected for pharmacokinetics and ECG assessments.

3.2 Hypothesis to be Tested

With respect to the primary endpoint Moderate to Severe CIPN at 9 months after first dose of IMP the statistical hypothesis to test is:

$$\mathrm{H}_0: \mu_{5\mu mol/kg} = \mu_{placebo}$$

$$\mathrm{H}_1: \mu_{5\mu mol/kg} \neq \mu_{placebo}$$

where μ_x represents the oxaliplatin-dose adjusted Moderate to Severe CIPN event rate at 9 months on treatment x. The treatment effect will be captured as the ratio of event rates, $\Psi = \mu_{5\mu mol/kg}/\mu_{placebo}$, so that the preceding null and alternative hypotheses can be reframed as

$$\mathrm{H}_0: \Psi = 1 \text{ versus } \mathrm{H}_1: \Psi \neq 1$$

A rate ratio <1 favours the PledOx 5µmol/kg group over placebo.

3.3 Handling of Dropouts or Missing Data

All reasonable efforts will be made to obtain complete data for all patients. However, missing observations may occur due to patients being lost to follow-up or non-compliant with the required protocol assessments.

Baseline

In all situations where baseline values are not recorded or not taken at the baseline visit (in most cases Cycle 1, Day 1), the value recorded from the last visit prior to Cycle 1 Visit will be used as the baseline value.

Handling of Incomplete Dates

Incomplete (partial or missing) dates will be presented in data listings as provided on the eCRF. However, for use in calculations (e.g. to calculate the duration of an AE or medication use) dates will be estimated as follows.

For partial start-dates:

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then:
  i) If the year matches the year of the first dose date, then impute the month and day of the first dose date.
  ii) Otherwise, assign 'January'.
- If the day is unknown, then:
  i) If the month and year match the month and year of the first dose date, then impute the day of the first dose date.
  ii) Otherwise, assign '01'.

For partial end-dates:

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then assign 'December'.
- If the day is unknown, then assign the last day of the month

If the above rules for end-dates result in an illogical date with regards to the dates the patient was in the study, then the end date will be replaced with the patient's date of completion/withdrawal. Furthermore, should the above rules not result in the most conservative date (as described below), then the imputed value may be replaced by a date that will lead to a more conservative analysis.

After implementing the rules above, to determine whether AEs with incomplete start or stop dates are non-treatment-emergent or treatment-emergent the following strategy will be used:

- If the start date and stop date are both missing, the most conservative approach is taken and the AE is considered to be treatment-emergent.
- If the start date is missing but the stop date is not missing and is on or after the day of first study drug administration then the most conservative approach is taken and the AE is considered to be treatment-emergent.
- If the start date is missing but the stop date is not missing and is before the day of first study drug administration then the AE is considered to be non-treatment-emergent.

If the date of first and/or last dose of study drug administration is missing then duration of exposure will be set to missing.

3.4 Handling of Unscheduled or Repeated Measurements

Descriptive summaries and by-visit analyses will be presented according to the planned (scheduled) visits, unless otherwise specified. Discontinuation visits will be summarised at a scheduled visit providing the discontinuation visit occurs within the protocol specified visit windows. The protocol specified visit windows are to be completed.

In case data collection is done at an Unscheduled Visit rather than at the planned Assessment Visit, that measurement will be allocated to the nearest Assessment Visit. This allocation will be implemented in the Reporting Data Base.

4. STUDY PATIENTS

Study Patients data will be presented by descriptive statistics by treatment group and total. Continuous variables will be summarised by number of patients (n), mean, standard deviation (SD), minimum, median and maximum, while categorical variables by counts and percentages. Unless otherwise stated the calculation of proportions will be based on the size of the analysis set of interest.

Listings will include all enrolled patients unless specified otherwise.

Summaries for Study Patients variables will be provided for both the mITT and the safety analysis set.

4.1 Patient Disposition

The number and percentage of all patients screened, randomised, randomised who did not receive IMP, included in the safety analysis set, included in the modified ITT analysis set, prematurely discontinued IMP, prematurely withdrawn from the study, and patients who completed the study will be presented by treatment group and total.

The number and percentage of patients will be summarised by their reasons for withdrawal (including Adverse Event, Death, Recurrent Disease, High Manganese Within the CNS, Lack of Efficacy, Lost to follow up, Non-Compliance With Study Drug, Physician Decision, Pregnancy, Progressive Disease, Protocol Deviation, Recovery, Site Terminated by Sponsor, Study Terminated by Sponsor, Technical Problems, Withdrawal by Subject, Other).

Individual reasons for withdrawal will be presented in the listing.

4.2 Protocol Deviations

All responses to the inclusion and exclusion criteria and all protocol deviations will be listed by patient. All important protocol deviations may also be summarised by treatment group, total for pre-specified categories, as appropriate.

4.3 Background and Demographic Characteristics

Summaries for background and demographic characteristics will be provided for both the mITT and the safety analysis set.

4.3.1 Demography

Demographic characteristics (age [years], gender [male, female] and race [Asian, Black or African American, White]) and body measurements (height, weight and BMI) collected at Screening will be summarised for each treatment group and total.

Age (years) is calculated in years as: integer(date of first dose of IMP – date of birth).

Body Mass Index (BMI) is calculated as: Weight (kg) / Height (m)^2.

4.3.2 Medical History, Ongoing Medical Conditions and Prior Anti-cancer Therapy

Medical history and ongoing medical conditions will be coded using the MedDRA Dictionary, Version 23.0. The number and percentage of patients will be presented for ongoing conditions and previous conditions separately by system organ class (SOC) and preferred term (PT) for each treatment group and total. Also, the number and percentage of patients with prior anti-cancer therapy will be presented for each treatment group and total. All events will be listed by patient.

4.3.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (WHODRUG GLOBAL B3 September 1, 2017). The number and percentage of patients will be presented for prior and concomitant medications separately by system organ class (SOC) and Anatomical Therapeutic Chemical (ATC) classification system for each treatment group and total. All events will be listed by patient.

4.3.4 ECOG Performance Status

The number and percentage of patients in the categories of the ECOG performance status (see Table 1) at baseline (time of administration of the first dose of IMP – day 1, cycle 1) will be presented by treatment group and total.

Table 1 ECOG Performance Status

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

4.3.5 ECG at Screening

The 12-lead electrocardiogram and QTcF interval is measured at screening only.

Data presentations

- Table: number (%) of patients with normal/abnormal ECG by treatment group and total.
- Table: descriptive statistics of QTcF by treatment group and total.

All observed values of the 12-lead ECG and QTcF will be listed by patient.

4.4 Administration of Investigational Medical Product and Chemotherapy

4.4.1 Investigational Medical Product (IMP)

The following variables related to the administration of IMP will be summarised and listed:

- Number and percentage of patients receiving IMP by cycle
- Cumulative dose of IMP
- Duration of IMP administration (weeks)
- Dose intensity (mL/week) = cumulative dose (mL) / treatment duration (weeks)
- Mean number of treatment cycles of IMP

Data presentations

- Table: number (%) of patients receiving IMP by treatment group and total for each treatment cycle
- Table: descriptive statistics of cumulative dose of IMP by treatment group and total
- Table: descriptive statistics of duration of IMP by treatment group and total
- Table: descriptive statistics of dose intensity of IMP by treatment group and total
- Table: descriptive statistics of number of treatment cycles of IMP by treatment group and total

All observed values of the administration of IMP will be listed by patient.

4.4.2 Oxaliplatin

The following variables related to the administration of oxaliplatin will be summarised and listed:

- Number and percentage of patients receiving oxaliplatin by cycle
- Cumulative dose of oxaliplatin (see also Section 5.3.3)
- Duration of oxaliplatin administration (weeks)
- Dose intensity (mg/m^2/week) = cumulative dose (mg/m^2) / treatment duration (weeks)
- Number and percentage of patients with dose modifications (reduced or delayed) of Oxaliplatin
- Duration of dose delay(s)
- Mean number of treatment cycles of Oxaliplatin

Data presentations

- Table: number (%) of patients receiving oxaliplatin by treatment group and total for each treatment cycle
- Table: descriptive statistics of cumulative dose of oxaliplatin by treatment group and total
- Table: descriptive statistics of duration of oxaliplatin by treatment group and total
- Table: descriptive statistics of dose intensity of oxaliplatin by treatment group and total
- Table: number (%) of patients with dose modifications (reduced or delayed) of oxaliplatin by treatment group and total for each treatment cycle
- Table: descriptive statistics of duration of dose delays of oxaliplatin by treatment group and total
- Table: descriptive statistics of number of treatment cycles of oxaliplatin by treatment group and total
- Figure: the proportion of patients receiving oxaliplatin will be graphically depicted (lineplot) vs treatment cycle/assessment visit by treatment group.

All observed values of the administration of oxaliplatin will be listed by patient.

4.4.3 5-FU

The following variables related to the administration of 5-FU (IV Bolus/IV Continued Infusion) will be summarised and listed:

- Number and percentage of patients receiving 5-FU by cycle
- Cumulative dose of 5-FU (see also Section 5.4.4)
- Duration of 5-FU administration (weeks)
- Dose intensity (mg/m^2/week) = cumulative dose (mg/m^2) / treatment duration (weeks)
- Number and percentage of patients with dose modifications (reduced or delayed) of 5-FU
- Duration of dose delay(s)
- Mean number of treatment cycles of 5-FU

Data presentations

- Table: number (%) of patients receiving 5-FU by treatment group and total for each treatment cycle
- Table: descriptive statistics of cumulative dose of 5-FU (IV Bolus/IV Continued Infusion) by treatment group and total
- Table: descriptive statistics of duration of 5-FU by treatment group and total
- Table: descriptive statistics of dose intensity of 5-FU (IV Bolus/IV Continued Infusion) by treatment group and total
- Table: number (%) of patients with dose modifications (reduced or delayed) of 5-FU by treatment group and total for each treatment cycle
- Table: descriptive statistics of duration of dose delays of 5-FU by treatment group and total
- Table: descriptive statistics of number of treatment cycles of 5-FU by treatment group and total

All observed values of the administration of 5-FU (IV Bolus/IV Continued Infusion) will be listed by patient.

4.4.4 Calcium-folinate or Calcium-levofolinate

The following variables related to the administration of Calcium-folinate or Calcium-levofolinate will be summarised and listed:

- Number and percentage of patients receiving Calcium-folinate or Calcium-levofolinate by cycle
- Cumulative dose of Calcium-folinate or Calcium-levofolinate
- Duration of Calcium-folinate or Calcium-levofolinate administration (weeks)
- Dose intensity (mg/m^2/week) = cumulative dose (mg/m^2) / treatment duration (weeks)
- Number and percentage of patients with dose modifications (reduced or delayed) of Calcium-folinate or Calcium-levofolinate
- Mean number of treatment cycles of Calcium-folinate or Calcium-levofolinate

Data presentations

- Table: number (%) of patients receiving Calcium-folinate or Calcium-levofolinate by treatment group and total for each treatment cycle
- Table: descriptive statistics of cumulative dose of Calcium-folinate or Calcium-levofolinate by treatment group and total
- Table: descriptive statistics of duration of Calcium-folinate or Calcium-levofolinate by treatment group and total
- Table: descriptive statistics of dose intensity of Calcium-folinate or Calcium-levofolinate by treatment group and total
- Table: number (%) of patients with dose modifications (reduced or delayed) of Calcium-folinate or Calcium-levofolinate by treatment group and total for each treatment cycle
- Table: descriptive statistics of number of treatment cycles of Calcium-folinate or Calcium-levofolinate by treatment group and total

All observed values of the administration of Calcium-folinate or Calcium-levofolinate will be listed by patient.

5. EFFICACY EVALUATION

Unless otherwise stated, all efficacy variables will be analysed using the mITT analysis set. The general principles for handling unscheduled or repeated measurements is described in Section 3.4.

5.1 Primary Endpoint

5.1.1 Moderate to Severe CIPN

The primary endpoint is defined as the proportion of patients (with moderate or severe chronic CIPN) scoring 3 or 4 in at least 1 of the first 4 items of the FACT/GOG-NTX-13 (i.e., FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet, 9 months after the first dose of IMP (i.e. PledOx or placebo administered on Day 1, Cycle 1 of mFOLFOX6 chemotherapy).

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Moderate to Severe CIPN will derived (SAS) as follows:

```
cipn=0;
IF ntx1_std=. AND ntx2_std=. AND ntx3_std=. AND ntx4_std=. THEN cipn=.;
ELSE IF ntx1_std IN('3','4') OR ntx2_std IN('3','4') OR
        ntx3_std IN('3','4') OR ntx4_std IN('3','4') THEN cipn=1;
```

Primary Analysis – Cochran-Mantel-Haenszel. The primary analysis of the primary endpoint Moderate to Severe CIPN (yes/no) at 9 months after first dose of IMP will be analysed by the Cochran-Mantel-Haenszel (CMH) estimate of the common relative risk of Moderate to Severe CIPN. The treatment effect will be assessed by estimating the ratio of the incidence rates of CIPN in PledOx 5µmol/kg versus Placebo along with its 95% confidence interval and corresponding p-value. The CMH estimate will be adjusted for cumulative exposure of oxaliplatin and stratified by study and region. Incidence rates (95% CIs) for each treatment will also be presented.

Notations. The combined analysis includes two studies (POLAR-A and POLAR-M) and two geographical regions (Asia/Non-Asia), and so there are 4 strata, where

1 = POLAR-A / Asia
2 = POLAR-A / Non-Asia
3 = POLAR-M / Asia
4 = POLAR-M / Non-Asia

Treatments are denoted by 1 and 2, where 1 = PledOx 5µmol/kg and 2 = Placebo. For treatment *j* in the *i*th strata the cumulative exposure of oxaliplatin is T_{ij} and E_{ij} is CIPN events. Let $T_{i\bullet} = T_{i1} + T_{i2}$ and $E_{i\bullet} = E_{i1} + E_{i2}$ denote total cumulative exposure of oxaliplatin and total CIPN events in the *i*th strata.

CMH point estimate of the common relative risk across strata. Under $H_0: R_1 = R_2 = R$, Breslow and Day [1] provide the stratified Cochran-Mantel-Haenszel estimate of the common relative risk as

$$\hat{R}_{M-H} = \frac{\sum_{i=1}^{k} \frac{E_{i1}T_{i2}}{T_{i\bullet}}}{\sum_{i=1}^{k} \frac{E_{i2}T_{i1}}{T_{i\bullet}}}$$

Also, Robins, Breslow and Greenland [2] provide an estimate of the variance of $\log \hat{R}_{M-H}$ as

$$\hat{V}\left[\log\left(\hat{R}_{M-H}\right)\right]=\frac{\sum_{i=1}^{k}\frac{T_{i1}T_{i2}E_{i\bullet}}{T_{i\bullet}^{2}}}{\hat{R}_{M-H}\left\{\sum_{i=1}^{k}\frac{T_{i1}T_{i2}E_{i\bullet}}{T_{i\bullet}\left(T_{i2}+T_{i1}\hat{R}_{M-H}\right)}\right\}^{2}}$$

Then, a 95% confidence interval for the common relative risk across strata is,

$$\exp\left\{log\left(\hat{R}_{M-H}\right)\pm 1.96\times SE\right\}$$

where $SE=\sqrt{\hat{V}\left[\log\left(\hat{R}_{M-H}\right)\right]}$.

The statistic $Z=\frac{log(\hat{R}_{M-H})}{SE}\sim N(0,1)$ so the 2-sided p-value is calculated by $2\times\left(1-CDF(|z|)\right)$.

CMH event rates for each treatment. The Cochran-Mantel-Haenszel oxaliplatin exposure weighted incidence rate estimate for treatment *j* across strata is given by

$U_j=\frac{\sum_{i=1}^{k}w_i\lambda_{ij}}{\sum_{i=1}^{k}w_i}$, j=1,2 and $\lambda_{ij}=\frac{E_{ij}}{T_{ij}}$ (i.e the event rate for treatment *j* in strata *i*) and

$w_i=\frac{2}{\frac{1}{T_{i1}}+\frac{1}{T_{i2}}}$ (i.e. the harmonic mean cumulative exposure of oxaliplatin in strata *i*).

CMH variance of the event rates. The variance of Cochran-Mantel-Haenszel oxaliplatin exposure weighted incidence rate estimate for treatment *j* across strata is given by

$$\mathrm{Var}\left[U_j\right]=\mathrm{Var}\left[\frac{\sum_{i=1}^{k}w_i\lambda_{ij}}{\sum_{i=1}^{k}w_i}\right]=\frac{\sum_{i=1}^{k}w_i^{2}\mathrm{Var}\left(\lambda_{ij}\right)}{\left(\sum_{i=1}^{k}w_i\right)^{2}}$$

and hence

$$\hat{\mathrm{Var}}\left[U_j\right]=\frac{\sum_{i=1}^{k}w_i^{2}\mathrm{Var}\left(\hat{\lambda}_{ij}\right)}{\left(\sum_{i=1}^{k}w_i\right)^{2}}=\frac{\sum_{i=1}^{k}w_i^{2}\frac{\hat{\lambda}_{ij}^{2}}{E_{ij}}}{\left(\sum_{i=1}^{k}w_i\right)^{2}}=\frac{\sum_{i=1}^{k}w_i^{2}\frac{E_{ij}}{T_{ij}^{2}}}{\left(\sum_{i=1}^{k}w_i\right)^{2}}$$

Further,

$$\mathrm{Var}\left[\log\left(U_j\right)\right]=\frac{1}{U_j^{2}}\mathrm{Var}\left[U_j\right]=\frac{\left(\sum_{i=1}^{k}w_i\right)^{2}}{\left(\sum_{i=1}^{k}w_i\lambda_{ij}\right)^{2}}\times\frac{\sum_{i=1}^{k}w_i^{2}\mathrm{Var}\left(\lambda_{ij}\right)}{\left(\sum_{i=1}^{k}w_i\right)^{2}}=\frac{\sum_{i=1}^{k}w_i^{2}\mathrm{Var}\left(\lambda_{ij}\right)}{\left(\sum_{i=1}^{k}w_i\lambda_{ij}\right)^{2}}$$

and so

$$\hat{\mathrm{V}}\mathrm{ar}\left[\log\left(\mathrm{U}_{\mathrm{j}}\right)\right]=\frac{\sum_{\mathrm{i}=1}^{\mathrm{k}}\mathrm{w}_{\mathrm{i}}^{2}\mathrm{Var}\left(\hat{\lambda}_{\mathrm{ij}}\right)}{\left(\sum_{\mathrm{i}=1}^{\mathrm{k}}\mathrm{w}_{\mathrm{i}}\hat{\lambda}_{\mathrm{ij}}\right)^{2}}=\frac{\sum_{\mathrm{i}=1}^{\mathrm{k}}\mathrm{w}_{\mathrm{i}}^{2}\frac{\hat{\lambda}_{\mathrm{ij}}^{2}}{\mathrm{E}_{\mathrm{ij}}}}{\left(\sum_{\mathrm{i}=1}^{\mathrm{k}}\mathrm{w}_{\mathrm{i}}\hat{\lambda}_{\mathrm{ij}}\right)^{2}}=\frac{\sum_{\mathrm{i}=1}^{\mathrm{k}}\mathrm{w}_{\mathrm{i}}^{2}\frac{\mathrm{E}_{\mathrm{ij}}}{\mathrm{T}_{\mathrm{ij}}^{2}}}{\left(\sum_{\mathrm{i}=1}^{\mathrm{k}}\mathrm{w}_{\mathrm{i}}\frac{\mathrm{E}_{\mathrm{ij}}}{\mathrm{T}_{\mathrm{ij}}}\right)^{2}}$$

Then, a 95% confidence interval for the Cochran-Mantel-Haenszel oxaliplatin exposure weighted incidence rate estimate across strata is,

$$U_j \times \exp\left\{\pm 1.96\sqrt{\widehat{Var}\left[log\left(U_j\right)\right]}\right\}$$

Interpretation of parameter estimates. The Cochran-Mantel-Haenszel method provide estimates of oxaliplatin-dose adjusted Moderate to Severe CIPN event rates at 9 months. The associated unit of measurement for the CMH estimates is therefore the CIPN event rate per unit dose of oxaliplatin. To aid in clinical interpretation and understanding, the CMH estimates will be scaled to a relevant clinical dose eg 800 mg/m^2 to allow the event rate to be expressed per 100 patients relative to this dose. It can also be used to represent the number of events saved when receiving active treatment as compared to placebo. The example data below illustrates this in more detail.

The exact same interpretation can be done for the event rates (LSmeans) estimated from the negative binomial model as described further below.

Table 2 Example data

	Placebo	**PledOx 5 µmol/kg**	
No CIPN	70 (59%)	86 (73%)	156
CIPN	48 (41%)	32 (27%)	80
	118	118	236

Table 3 Example data: Cochran-Mantel-Haenszel estimates of Moderate to severe CIPN 9 months after first dose of IMP

	N	**Estimate**	**95% CI**	**P-value**
PledOx 5 µmol/kg	118	0.000317	[0.000222; 0.000454]	-
Placebo	118	0.000462	[0.000343; 0.000623]	-
PledOx 5 µmol/kg vs Placebo	236	0.6869	[0.4391; 1.0745]	0.0999

Suppose the mean cumulative dose overall of oxaliplatin is 800 mg/m^2 so the event rates are estimated by:

PledOx 5 µmol/kg 0.000317 x 800 = 0.25 CIPN events per patient per 800 mg/m^2 of oxaliplatin

Placebo 0.000462 x 800 = 0.37 CIPN events per patient per 800 mg/m^2 of oxaliplatin

This translates into:

PledOx 5 µmol/kg 25 CIPN events per 100 patients treated

Placebo 37 CIPN events per 100 patients treated

This represents a saving of 12 CIPN events per 100 patients treated with PledOx 5 µmol/kg.

In the results presentation of the CSR the observed mean cumulative dose of oxaliplatin will be used.

Supportive Analysis of the primary endpoint - Negative Binomial Regression. A supportive analysis of the primary endpoint Moderate to Severe CIPN (yes/no) at 9 months after first dose of IMP will be analysed by a negative binomial regression model adjusted for study (POLAR-A / POLAR-M) and region (Asia / non-Asia). An offset variable will also be used to adjust for the oxaliplatin exposure defined as the logarithm of the cumulative dose of oxaliplatin received by each patient. Estimate of the treatment contrast (rate ratio) and its corresponding 95% confidence interval will be based on the anti-log of the model parameter estimate and CI.

SAS Code Example Negative Binomial Regression using PROC GENMOD

```
PROC GENMOD;
  CLASS study region trt;
  MODEL cipn = study region trt/DIST=negbin LINK=log SCALE=deviance OFFSET=log_exp;
  ESTIMATE 'PledOx 5 µmol/kg vs Placebo' trt 1 -1;
  LSMEANS trt / CL EXP;
RUN;
```

If convergence criterion is not met using PROC GENMOD an alternative using PROC NLMIXED will be used.

SAS Code Example Negative Binomial Regression using PROC NLMIXED

```
PROC NLMIXED;
  PARMS b0 -2 b1 .1 b2 -.01 b3 .1 phi .1;
  eta = log_exp + b0 + b1*(study=1) + b2*(region=1) + b3*(trt=0);
  mu = exp(eta);
  LL = y*log(phi*mu) - (y+(1/phi))*log(1+(phi*mu)) + lgamma(y+(1/phi)) -
lgamma(1/phi) - lgamma(y+1);
  MODEL y ~ general(LL);
RUN;
```

Exploratory Analysis – Exact Logistic Regression. An exploratory analysis of the primary endpoint Moderate to Severe CIPN at 9 months after first dose of IMP will be analysed by exact logistic regression model adjusted for study (POLAR-A / POLAR-M) and region (Asia / non-Asia). Estimate of the treatment effect and its corresponding 95% confidence interval will be based on the odds-ratio.

SAS Code Example Exact Logistic Regression

```
PROC LOGISTIC DESC;
       CLASS study region trt(ref='0: Placebo');
       MODEL cipn = study region trt;
       EXACT trt;
RUN;
```

Using the same example data presented above, a crude estimate of the odds-ratio then is:

(0.27/0.73) / (0.41/0.59) = 0.53

Table 4 Example data: Exact Logistic Regression of Moderate to severe CIPN 9 months after first dose of IMP

	N	CIPN (%)	Odds-ratio	95% CI	P-value
PledOx 5 µmol/kg	118	27.1	-	-	-
Placebo	118	40.7	-	-	-
PledOx 5 µmol/kg vs Placebo	236	-	0.54	[0.31;0.94]	0.0293

Data Presentations

- Table: the primary analysis of Moderate to Severe CIPN based on the Cochran-Mantel-Haenszel estimate will be presented by number of patients (N), treatment estimates and its 95% CIs. The rate ratio between PledOx 5 µmol/kg and Placebo will be presented by the estimate, 95% CI and p-value.
- Table: the supportive analysis of Moderate to Severe CIPN based on the negative binomial regression model will be presented by number of patients (N), treatment estimates and its 95% CIs. The rate ratio between PledOx 5 µmol/kg and Placebo will be presented by the estimate, 95% CI and p-value.
- Table: the number and percentage of patients with Moderate to Severe CIPN along with its 95% CI presented by treatment group and total for each treatment visit/assessment visit. The confidence intervals will be based on the method of Clopper-Pearson (exact).
- Table: the exploratory analysis of Moderate to Severe CIPN based on the exact logistic regression model will be presented by number of patients (N), number of patients (%) with Moderate to Severe CIPN at 9 months after first does of IMP for each treatment group, and odds-ratio, 95% CI and p-value for the treatment comparison.
- Figure: the proportion (including 95% CIs) of patients with Moderate to Severe CIPN will be graphically depicted (lineplot) vs treatment cycle/assessment visit by treatment group.
- All observed values of Moderate to Severe CIPN will be listed by patient.

Missing values of the primary endpoint will be handled as described in Section 5.2.

5.2 Handling of Missing Data in the Primary Endpoint

For the primary endpoint Moderate to Severe CIPN (yes/no) the following methods of imputation will be used for the primary analysis in case of missing:

1. Observed cases (no imputation)
2. "Non-responder" if missing (ie 3 or 4 on FACT/GOG)
3. Tipping point analysis – combinations of missing data values that would change the conclusion. References eg Yan (2009), Rubin (2012)

A tipping point analysis assesses the potential impact of informative missingness by progressively penalizing patients with missing data in the experimental arm. The goal is to find the level of penalization that results in loss of statistical significance on the primary endpoint.

The steps to perform the tipping point analysis are as follows:

1. The NB model as described in Section 5.1.1 is applied to each randomised treatment arm separately based on the observed data in that arm. This will give two parameters for each of the experimental and control groups, the event rate, μ, and the dispersion rate, κ.
2. For each subject, i, in the experimental arm who had t_i < 9 months follow-up and who did not record a primary endpoint event in the period $(0 - t_i]$, simulate their event rate, μ_i, by randomly sampling an observation from a $Gamma(shape = 1/\kappa, scale = 1/(\kappa\mu))$ distribution.
3. Using μ_i, the time to event for subject i in the period $(t_i, 9]$ is given by $\Delta_i = -\ln(1-\omega_i)/\mu_i$ where ω_i is a random deviate from a $U(0,1)$ distribution.
4. If $t_i + \Delta_i \leq 9$ then subject i is considered to have had an event at with an exposure time of $t_i + \Delta_i$. If $t_i + \Delta_i > 9$ then subject i is considered not to have event at with an exposure time of 9 months.
5. Steps 2-4 will result in a full dataset with no missing primary endpoint data over the period (0-9] months.

6. This full dataset is then analysed in the same manner as described for the primary endpoint using the Cochran-Mantel-Haenszel approach and the treatment effect and associated SE are estimated.
7. Steps 2-6 are repeated multiple times and the resulting treatment effect estimates and SEs are combined in SAS via PROC MIANALYZE using Rubin's rules. This will provide the estimated treatment effect having imputed missing data under a missing at random assumption.
8. Return to Step 2 and now, for each subject, i, in the experimental arm who had t_i < 9 months follow-up and who did not record a primary endpoint event in the period $(0 - t_i]$, resimulate their event rate, μ_i, by randomly sampling an observation from a $Gamma(shape = 1/\kappa, scale = 1/(\kappa(\mu + \varepsilon))$ distribution where ε is some small, positive number. Imputation of control treated patients is unchanged.
9. Repeat Steps 2-7. This will provide the estimated treatment effect having imputed missing data under a missing not at random with the event rate on experimental penalised by the amount ε.
10. Repeat steps 2-9 for penalising the experimental event rate by $\varepsilon, 2\varepsilon, 3\varepsilon, \ldots$ until statistical significance is lost.

5.3 Secondary Efficacy Endpoints

5.3.1 Mild to Severe CIPN

Proportion of patients (with mild, moderate or severe chronic CIPN) scoring 2, 3, or 4, in at least 1 of the first 4 items of the FACT/GOG-NTX-13 (i.e. FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet, 9 months after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Mild to Severe CIPN will derived (SAS) as follows:

```
cipn2=0;
IF ntx1_std=. AND ntx2_std=. AND ntx3_std=. AND ntx4_std=. THEN cipn2=.;
ELSE IF ntx1_std IN('2','3','4') OR ntx2_std IN('2','3','4') OR
        ntx3_std IN('2','3','4') OR ntx4_std IN('2','3','4') THEN cipn2=1;
```

Mild to Severe CIPN will be analysed using the method of Cochran-Mantel-Haenszel as described in detail in Section 5.1.1.

Data Presentations

- Table: the analysis of Mild to Severe CIPN based on the negative binomial regression model will be presented by number of patients (N), treatment estimates and its 95% CIs. The rate ratio between PledOx 5 µmol/kg and Placebo will be presented by the estimate, 95% CI and p-value.
- Table: the number and percentage of patients with Mild to Severe CIPN along with its 95% CI presented by treatment group and total for each treatment visit/assessment visit. The confidence intervals will be based on the method of Clopper-Pearson (exact).
- Figure: the proportion (including 95% CIs) of patients with Mild to Severe CIPN will be graphically depicted (lineplot) vs treatment cycle/assessment visit by treatment group.
- All observed values of Mild to Severe CIPN will be listed by patient.

All the analyses of Mild to Severe CIPN will be based on the observed cases. Hence, no imputation of missing values will be done.

5.3.2 Cold Sensitivity

Mean change from baseline in sensitivity to touching cold items on day 2, Cycle 4 of mFOLFOX6 chemotherapy, as assessed by the Cold Sensitivity questionnaire (ordinal scale 0-10).

Baseline is defined as the Screening measurement.

Analysis of Covariance. Cold Sensitivity will be analysed by Analysis of Covariance (ANCOVA) using the cold sensitivity baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data Presentations

- Table: the analysis cold sensitivity based on the ANCOVA model will be presented by number of patients (N), estimate (LSM) and 95% CI for each treatment group. The treatment contrast (PledOx 5 µmol/kg vs Placebo) will be presented by estimate (difference in LSM), 95% CI and p-value.
- Table: descriptive statistics of observed values of cold sensitivity by treatment and total for each visit (baseline (screening), cycle 2,4 and 8) and measurements within each treatment visit (pre-infusion day 1, post-infusion day 1, post-infusion day 2 and, post-infusion day 3).
- Figure: shift plot (with jitter) of cold sensitivity at baseline vs cycle 4, day 2

The same output (except for the ANCOVA analysis) will be produced also for the other 3 variables included in the Cold Sensitivity questionnaire:

- Swallowing cold liquids
- Throat discomfort
- Muscle cramps

5.3.3 Cumulative Dose of Oxaliplatin

Mean cumulative dose of oxaliplatin administered per patient during mFOLFOX6 chemotherapy, 9 months after the first dose of IMP. Summary statistics of oxaliplatin related variables are presented in Section 4.4.2.

In case the patient receives more than 12 cycles of oxaliplatin, that will also be accounted for when deriving the cumulative dose.

Analysis of Variance. Mean cumulative dose of oxaliplatin will be analysed by Analysis of Variance (ANOVA) using study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentation

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).

All observed values of mean cumulative dose of oxaliplatin will also be listed by patient.

5.3.4 Vibration Sensitivity Test

Mean change from baseline in vibration sense (0-8 ordinal scale), on the lateral malleolus (left and right), using a graduated tuning fork, at 9 months after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Vibration sense will be analysed by Analysis of Covariance (ANCOVA) using the vibration sense baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region

(Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo)
- Table: descriptive statistics of observed values by treatment and total for each treatment cycle
- Table: descriptive statistics of change from baseline by treatment and total for each treatment cycle
- Figure: shift plot (using jitter) of baseline vs 9-month assessment visit

All observed values of Vibration Sensitivity Test will also be listed by patient.

5.3.5 Pain (NRS)

Mean change from baseline in worst pain in hands or feet in the past week, using a numerical rating scale (NRS), at 9 months after the first dose of IMP. NRS is measured on an ordinal scale 0-10.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Pain will be analysed by Analysis of Covariance (ANCOVA) using the pain baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).
- Table: descriptive statistics of observed values by treatment and total for each treatment cycle.
- Table: descriptive statistics of change from baseline by treatment and total for each treatment cycle.
- Figure: shift plot (using jitter) of baseline vs 9-month assessment visit.

All observed values of worst pain in hands or feet will also be listed by patient.

5.3.6 Grooved Pegboard

Mean change from baseline in the time (seconds) to complete the Grooved Pegboard with the non-dominant hand, at 9 months after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Grooved pegboard will be analysed by Analysis of Covariance (ANCOVA) using the grooved pegboard baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).
- Table: descriptive statistics of observed values by treatment and total for each treatment cycle.
- Table: descriptive statistics of change from baseline by treatment and total for each treatment cycle.
- Figure: shift plot (using jitter) of baseline vs 9-month assessment visit.

- Figure: scatter plot (using jitter) by treatment group for each treatment cycle.

All observed values of grooved pegboard will also be listed by patient.

5.3.7 Long-term Moderate to Severe CIPN

Long-term Moderate to Severe CIPN is defined as the proportion of patients scoring 3 or 4 in at least 1 of the first 4 items of the FACT/GOG-NTX-13 (i.e. FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet 12 months after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Moderate to Severe CIPN will derived (SAS) as follows (same as primary endpoint):

```
cipn=0;
IF ntx1_std=. AND ntx2_std=. AND ntx3_std=. AND ntx4_std=. THEN cipn=.;
ELSE IF ntx1_std IN('3','4') OR ntx2_std IN('3','4') OR
        ntx3_std IN('3','4') OR ntx4_std IN('3','4') THEN cipn=1;
```

Long-term Moderate to Severe CIPN will be analysed using the method of Cochran-Mantel-Haenszel as described in detail in Section 5.1.1.

All the analyses of Long-term Moderate to Severe CIPN will be based on observed cases. Hence, no imputation of missing values will be done.

Data Presentations

- Table: the analysis of Long-term Moderate to Severe CIPN based on the negative binomial regression model will be presented by number of patients (N), treatment estimates and its 95% CIs. The rate ratio between PledOx 5 µmol/kg and Placebo will be presented by the estimate, 95% CI and p-value.

5.4 Exploratory Endpoints

5.4.1 Any CIPN

Any CIPN is defined as the proportion of patients with any CIPN scoring 1, 2, 3 or 4, in any of the first 4 items of the FACT/GOG-NTX-13 (i.e. FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet, at all other timepoints after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Any CIPN will derived (SAS) as follows:

```
cipn3=0;
IF ntx1_std=. AND ntx2_std=. AND ntx3_std=. AND ntx4_std=. THEN cipn3=.;
ELSE IF ntx1_std IN('1','2','3','4') OR ntx2_std IN('1','2','3','4') OR
        ntx3_std IN('1','2','3','4') OR ntx4_std IN('1','2','3','4') THEN
cipn3=1;
```

Data Presentations

- Table: the number and percentage of patients with Any CIPN along with its 95% CI presented by treatment group and total for each treatment visit/assessment visit. The confidence intervals will be based on the method of Clopper-Pearson (exact)
- Figure: the proportion (including 95% CIs) of patients with Any CIPN will be graphically depicted (lineplot) vs treatment cycle/assessment visit by treatment group.
- All observed values of Any CIPN will be listed by patient

The analysis of Any CIPN will be based on observed cases. Hence, no imputation of missing values will be done.

5.4.2 Mean Score of FACT/GOG NTX1-4

Mean score of the first 4 items of the FACT/GOG-NTX-13 (i.e. FACT/GOG-NTX-4), at 9 months after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Mean score of FACT/GOG NTX1-4 will be analysed by Analysis of Covariance (ANCOVA) using the baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).
- Table: descriptive statistics of observed values by treatment and total for each treatment cycle.
- Table: descriptive statistics of change from baseline by treatment and total for each treatment cycle.
- Figure: shift plot of baseline vs 9-month assessment visit.

All observed values of the Mean Score of FACT/GOG NTX1-4 will also be listed by patient.

5.4.3 Mean Score of FACT/GOG NTX1-13

Endpoint. Mean score of the 13 items of the FACT/GOG-NTX-13, at 9 months after the first dose of IMP.

Baseline. Defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Mean score of FACT/GOG-NTX-13 will be analysed by Analysis of Covariance (ANCOVA) using the baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).
- Table: descriptive statistics of observed values by treatment and total for each treatment cycle.
- Table: descriptive statistics of change from baseline by treatment and total for each treatment cycle.
- Figure: shift plot of baseline vs 9-month assessment visit.

All observed values of the Mean Score of FACT/GOG NTX1-13 will also be listed by patient.

5.4.4 Cumulative Dose of 5-FU

Endpoint. Mean cumulative dose of 5-FU (IV Bolus/IV Continued Infusion) administered per patient during mFOLFOX6 chemotherapy, 9 months after the first dose of IMP. Summary statistics of 5-FU related variables are presented in Section 4.4.3.

In case the patient receives more than 12 cycles of 5-FU, that will also be accounted for when deriving the cumulative dose.

Analysis of Variance. Mean cumulative dose of 5-FU will be analysed by Analysis of Variance (ANOVA) using study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented. In case the distribution of the endpoint deviates from normality the endpoint will be log-transformed and the inference will be based on the geometric mean, ratio of geometrics means and corresponding 95% CIs.

Data presentation

- Table: ANOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).

All observed values of mean cumulative dose of 5-FU will also be listed by patient.

5.4.5 Pharmacokinetics

The PK population (POLAR-M only) includes a subset of patients at pre-selected sites in all participating regions, where blood samples will be collected for pharmacokinetic assessments. Blood samples to measure plasma concentrations of PledOx will be taken pre-dose, 6 min post-dose, 15 min post-dose, 30 min post-dose, 60 min post-dose, and 240 min post-dose at treatment visit 1, 4 and 8. In addition, the PK parameters C_{max}, t_{max}, $AUC_{0\text{-}last}$ of PledOx will be derived.

Values below LLOQ will be set to LLOQ/2.

Data presentations

- Table: descriptive statistics of plasma concentrations of PlexOx by visit and time point.
- Table: descriptive statistics of pharmacokinetic parameters of PlexOx.
- Graph: mean plasma concentrations of PledOx by time for each cycle.

The analyses will be done on the PK population. All observed values of plasma concentrations and PK parameters of PledOx will also be listed by patient.

5.4.6 ECG QT/QTc

Mean QT/QTc interval using a 12-lead ECG at all measured time points.

The ECG variables is measured pre- and post-dose at cycle 1, 4 and 8, and at the End of Treatment visit. Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

ECG variables:

- ECG Mean heart rate
- Interpretation
- PR interval
- QRS duration
- QT interval
- QTcB interval
- QTcF interval
- RR interval

Data presentations

- Table: number (%) of patients with abnormal ECG by visit and time point.
- Table: descriptive statistics of each continuous ECG variable by visit and time point.

The ECG analyses will be done on the PK population. All observed values of the ECG variables will also be listed by patient.

5.4.7 EQ-5D-5L and Health VAS Score

Mean EQ-5D-5L health index and Health VAS score at 9 and 12 months after the first dose of IMP.

EQ-5D-5L Health Index. The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. It is often referred to as a Quality of Life (QoL) questionnaire. The EQ-5D-5L comprises 5 dimensions of health:

- Mobility
- Ability to self-care
- Ability to undertake usual activities
- Pain and discomfort
- Anxiety and depression

There are 5 options (levels, ordinal scale) under each dimension.

Endpoint. Mean health index is defined as the mean value of the 5 dimensions of the EQ-5D-5L questionnaire and will be analysed 9 and 12 months after the first dose of IMP, respectively.

Baseline. Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Mean health index will be analysed by Analysis of Covariance (ANCOVA) using the baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).
- Table: descriptive statistics of observed values by treatment and total
- Table: descriptive statistics of change from baseline by treatment and total

All observed values of Mean Health Index and Mean VAS Score will also be listed by patient.

Endpoint. Health VAS Score, the patient health status is also measured on a Visual Analogue Scale (VAS) ranging from 0 to 100, where 100 means best health and 0 worst health.

Baseline. Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Health VAS score will be analysed by Analysis of Covariance (ANCOVA) using the baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).
- Table: descriptive statistics of observed values by treatment and total
- Table: descriptive statistics of change from baseline by treatment and total

All observed values of Health VAS Score will also be listed by patient.

Endpoint. Number and percentage of patients by level of severity of the 5 dimensions of the EQ-5D-5L questionnaire.

Baseline. Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Data presentations

- Table: Number and percentage (%) of patients by level of severity of the 5 dimensions of the EQ-5D-5L questionnaire by treatment, total and visit

All observed values of the level of severity of the 5 dimensions of the EQ-5D-5L questionnaire will also be listed by patient.

5.4.8 Long-term Grooved Pegboard

Mean change from baseline in the time (seconds) to complete the Grooved Pegboard, with the non-dominant hand, at 12 months after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Long-term grooved pegboard will be analysed by Analysis of Covariance (ANCOVA) using the baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).
- Table: descriptive statistics of observed values by treatment and total for each treatment cycle.
- Table: descriptive statistics of change from baseline by treatment and total for each treatment cycle.
- Figure: shift plot (using jitter) of baseline vs 12-month assessment visit.

All observed values of Grooved Pegboard will also be listed by patient.

5.4.9 Long-term Pain (NRS)

Mean change from baseline in worst pain in hands or feet in the past week, using a NRS, at 12 months after the first dose of IMP. NRS is measured on an ordinal scale 0-10.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Analysis of Covariance. Long-term pain will be analysed by Analysis of Covariance (ANCOVA) using the baseline value as a continuous covariate and study (POLAR-A / POLAR-M), region (Asia / non-Asia) and treatment as factors. Least square means and its corresponding 95% confidence intervals will be presented.

Data presentations

- Table: ANCOVA analysis - Number of patients (N), Point Estimate (LSM), 95% CI and P-value by treatment group/treatment comparison (PledOx 5 µmol/kg vs Placebo).
- Table: descriptive statistics of observed values by treatment and total for each treatment cycle.
- Table: descriptive statistics of change from baseline by treatment and total for each treatment cycle.
- Figure: shift plot (using jitter) of baseline vs 12-month assessment visit.

All observed values of worst pain in hands or feet will also be listed by patient.

5.4.10 Change in Pain (NRS)

The proportion of patients with a 2-point, 3-point and 4-point increase vs baseline in worst pain in hands or feet in the past week using NRS at 9 and 12 months after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Exact Logistic Regression. The proportion of patients with a 2-point, 3-point and 4-point increase from baseline in worst pain in hands or feet will be analysed by an exact logistic regression model adjusted for study (POLAR-A / POLAR-M) and region (Asia / non-Asia). Estimate of the treatment effect and its corresponding 95% confidence interval will be based on the odds-ratio.

Data presentations

- Table: number and percentage of patients having a 2-point, 3-point and 4-point increase in worst pain in hands or feet based on the exact logistic regression model will be presented by number of patients (N), number of patients (%) with 2-point, 3-point and 4-point increase in worst pain in hands or feet at 9 and 12 months after first does of IMP, respectively for each treatment group, and odds-ratios, 95% CIs and p-values for the treatment comparisons.

All values will also be listed by patient.

The analyses will be based on the observed cases. Hence, no imputation of missing values will be done.

5.4.11 Health Economic Impact

Health economic impact, measured by the combined impact of medical resource utilization (hospitalizations, outpatient visits, medical procedures and medical use), patient impact (AEs, fall accidents, functional loss) and indirect societal costs (loss of ability to work), at 6 and 12 months after the first dose of IMP.

Baseline is defined as the time of administration of the first dose of IMP (Day 1, Cycle 1).

Data presentations

All health economic variables will be presented by summary statistics (including change from baseline where appropriate) by treatment group and total for each visit.

All observed values of health economic impact will also be listed by patient.

6. SAFETY EVALUATION

All safety evaluations will be performed on the safety analysis set unless specified otherwise.

6.1 Adverse Events

Adverse events will be recorded in the eCRF and will be coded according to the MedDRA dictionary Version 23.0. All AEs including SAEs will be collected up to 30 days after the last administration of IMP (or as of March 2nd., 2020, up to 30 days after the EOT) and followed until resolution.

A treatment-emergent adverse event (TEAE) is defined as an adverse event that started or worsened after the start of the administration of IMP. Treatment-emergent AEs will include AEs that occur after the first dose of IMP (i.e. day 1, Cycle 1) and end at the EOT visit (i.e. 14 days after the last dose of IMP). AEs will also be considered treatment-emergent if they are ongoing at first IMP infusion or start ≤30 days after the last dose of IMP. Adverse events with unknown start date/time will be assumed to be treatment-emergent unless the end date/time is known to be before administration of the first dose of IMP. Non-treatment emergent AEs will include any AEs that occur between informed consent and the first dose of IMP.

Allocation of AEs to study periods

All AEs and SAEs will be allocated to a study period depending on the onset date in relation to the date of administration of IMP:

Period 1: Time of informed consent until time before first dose of IMP (non-TEAE)

Period 2: Time of first dose of IMP until time of last dose of IMP + 30 days (TEAE)

Period 3: Time of last dose of IMP + 31 days and onwards (non-TEAE)

In case of complete or partial missing start or end date of an AE see details in Section 3.3.

Causality to the Investigational Medical Product (IMP)

- Not related
- Unlikely related
- Possibly related
- Probably related
- Definitely related

An AE/SAE is defined as related to IMP if the event is classified as Possibly, Probably or Definitely related.

Intensity of Adverse Events

- Mild
- Moderate
- Severe
- Life-threatening
- Death related to AE

No summaries will be done of AE/SAE by intensity but will be included in the listings.

Data presentations

If a patient experienced more than one TEAE the patient will be counted once for each SOC and once for each PT. System organ class and preferred terms will be ordered alphabetically first by SOC and then all PTs alphabetically within a SOC. Non-TEAEs will not be presented in summary tables, only in listings.

Tables: treatment-emergent AEs

- Number and percentage of patients experiencing TEAEs by SOC and PT for each treatment group and total
- Number and percentage of patients experiencing TEAEs leading to withdrawal of IMP by SOC and PT for each treatment group and total
- Number and percentage of patients experiencing TEAEs related to IMP by SOC and PT for each treatment group and total
- Number and percentage of patients experiencing TEAEs leading to death by SOC and PT for each treatment group and total

Tables: Serious treatment-emergent AEs

- Number and percentage of patients experiencing Serious TEAEs by SOC and PT for each treatment group and total
- Number and percentage of patients experiencing Serious TEAEs leading to withdrawal of IMP by SOC and PT for each treatment group and total

- Number and percentage of patients experiencing Serious TEAEs related to IMP by SOC and PT for each treatment group and total

All AEs will be listed by patient including subject-id, treatment group, AE Term, SOC, PT, Time of onset (in relation to first dose of IMP), time of resolution (in relation to first dose of IMP), Intensity, Causality, Action taken, Outcome and a flag for TEAE/non-TEAE. The following listings will be provided:

- All AEs (including SAEs)
- All SAEs
- All AEs leading to withdrawal of IMP
- All AEs leading to hospitalization
- All AEs leading to death

6.1.1 Adverse Events of Special Interest

AEs/SAEs of special interest are selected based on following SMQs from the Medical Dictionary for Regulatory Activities (MedDRA):

- Convulsions
- Neuropathy
- Hypersensitivity

Data presentations

- Table: Number and percentage of patients with Convulsions, Neuropathy or Hypersensitivity related AEs by SOC and PT for each treatment group and total
- Table: Number and percentage of patients with Convulsions, Neuropathy or Hypersensitivity related SAEs by SOC and PT for each treatment group and total

Chemotherapy-related AEs/SAEs recorded in the eCRF are also of special interest. Examples of such events are peripheral sensory neuropathy, hematological toxicities, ANC, febrile neutropenia, WBC count and thrombocytopenia.

Data presentations

- Table: Number and percentage of patients with chemotherapy-related AEs by SOC and PT for each treatment group and total
- Table: Number and percentage of patients with chemotherapy-related SAEs by SOC and PT for each treatment group and total

IMP toxicity-related AEs/SAEs are recorded in the eCRF defined as an AE that is considered to be chemotherapy-related toxicity and also is possibly, probably or definitely related to the IMP treatment using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

In SAS IMP toxicity will be derived as:

```
imp_tox=0;
IF aechemtx EQ 'Yes' AND aerel IN('Definitely Related',
                                  'Possibly Related',
                                  'Probably Related') THEN imp_tox=1;
```

where,

- aechemtx = Is this AE considered to be chemotherapy-related toxicity?
- aerel = Is there a reasonable possibility of a causal relationship between the IMP treatment and the AE?

A patient is counted only once in case of multiple events for a given patient.

Data presentations

- Table: Number and percentage of patients with IMP toxicity-related AEs by SOC and PT for each treatment group and total
- Table: Number and percentage of patients with IMP toxicity-related SAEs by SOC and PT for each treatment group and total

6.2 Laboratory Evaluation

Laboratory testing will be performed at each visit just before IMP administration. Local laboratories will be used to analyse the samples, and the local units will be standardised using SI-units for all reporting of laboratory tests.

Hematology

Hematology test will be performed at screening, treatment visit 1-12, End of Treatment visit, and assessment visit 1-8. The following hematology tests will be performed:

Hematology Test	SI-unit
Hemoglobin	g/L
Leukocytes	10^9/L
Neutrophils (Differential)	%
Lymphocytes (Differential)	%
Monocytes (Differential)	%
Eosinophils (Differential)	%
Basophils (Differential)	%
Neutrophils (absolute)	10^9/L
Erythrocytes (absolute)	10^12/L
Platelet	10^9/L

Biochemistry

Biochemistry test will be performed at screening, treatment visit 1, 4, 8, 12 and End of Treatment visit. The following biochemistry tests will be performed:

Biochemistry Test	SI-unit
Alkaline Phosphatase (ALP)	IU/L
Total Bilirubin	umol/L
Alanine Aminotransferase (ALT)	IU/L
Aspartate Aminotransferase (AST)	IU/L
Creatinine	umol/L
Albumin	g/L

Baseline

For hematology and biochemistry laboratory tests baseline is defined as the sample taken prior to first dose of IMP. In case of missing, the screening measurement will be used instead.

Derived variables

- For all laboratory tests change from baseline will derived for all post-baseline measurements.
- A laboratory value marked as LLOQ or having a registered value <LLOQ will be imputed by LLOQ/2. In case >50% of the values at a timepoint are <LLOQ the mean will be set to LLOQ.

Values outside normal ranges

Laboratory values outside the normal ranges will be flagged in the laboratory report. For each flagged value the Investigator should mark the value as "Clinically Significant" (CS) or "Not Clinically Significant" (NCS).

Data presentations

- Table: for each laboratory test, descriptive statistics of observed values by treatment group, total and by treatment/assessment visit.
- Table: for each laboratory test, descriptive statistics of change from baseline by treatment group, total and by treatment/assessment visit.
- Figure: for each laboratory test, scatterplot (using jitter) of observed values by treatment group and treatment/assessment visit.
- Table: for each laboratory test, number and percentage of patients with clinically significant values outside normal ranges by treatment group and treatment/assessment visit.

All laboratory tests will be listed and patients with clinically significant (according to the Investigator's criteria) abnormal values (out of normal range reported by the laboratory) will be flagged and listed separately. Significant findings made after drug administration that meet the definition of an AE must be reported under the AE section.

6.3 Blood Manganese

Blood samples will be collected for assessment of manganese (Mn) at screening, treatment cycle 4, 8, 12 and End of Treatment. Blood manganese are available in both ug/L and nmol/L. The latter will be used in the summary tables and listings.

Baseline

Baseline is defined as the measurement at screening.

Derived variables

- Change from baseline will derived for all post-baseline measurements.
- Indicator variable if blood manganese is >2xULN.

Data presentations

- Table: descriptive statistics of observed values by treatment group, total and by treatment visit.
- Table: descriptive statistics of change from baseline by treatment group, total and by treatment visit.
- Figure: scatterplot (using jitter) of observed values by treatment group and treatment visit.
- Table: number and percentage of patients with blood manganese values >2xULN by treatment group and treatment visit.

All blood Mn results for individual patients will be listed and patients with clinically significant (according to the Investigator's criteria) abnormal values (out of normal range reported by the laboratory) will be flagged and listed separately.

6.4 Brain MRI and Neurologic Examination

Monitoring of increased Mn levels and/or Parkinson-like symptoms will be performed. Any patient who has elevated Mn levels (>2xULN) confirmed by MRI that shows Mn accumulation should be immediately withdrawn from further treatment with the IMP.

Patients that show Mn concentrations >2xULN before Cycle 5 or Cycle 9 will be referred to a brain MRI investigation and a neurological examination. If the MRI is positive (i.e. T1-weighted images (MRI intensity) and T1 images in the globus pallidus), the patient will be discontinued from the study and followed every 3 months until resolution (i.e. MRI intensity is low/none).

Blood for Mn assessment will also be taken in the case of Parkinson-like symptoms. If the Mn level is >2xULN, an MRI of the brain should be performed (as above). If the Mn level is ≤2xULN then the patient can continue in the study according to the protocol.

Any results from MRI scan and neurological examinations following an elevated (>2x ULN) blood Mn will be listed per patient.

6.5 Vital Signs

Vital signs variables include:

- Resting pulse (beats per minute)
- Resting systolic blood pressure (mmHg)
- Resting diastolic blood pressure (mmHg)

Baseline

For vital signs baseline is defined as the sample taken prior to first dose of IMP. In case of missing, the screening measurement will be used instead.

Derived variables

For all vital signs change from baseline will derived for all post-baseline measurements.

Data presentations

- Table: for each vital sign variable, descriptive statistics of observed values by treatment group, total and by treatment/assessment visit.
- Table: for each vital sign variable, descriptive statistics of change from baseline by treatment group, total and by treatment/assessment visit.

All vital signs variables will be listed by patient.

6.6 Weight and BMI

Baseline

For both weight and BMI baseline is defined as the sample taken prior to first dose of IMP. In case of missing, the screening measurement will be used instead.

Derived variables

- Body Mass Index (BMI) is calculated as: Weight (kg) / Height $(m)^2$.
- For both weight and BMI change from baseline will derived for all post-baseline measurements.

Data presentations

- Table: for both weight and BMI, descriptive statistics of observed values by treatment group, total and by treatment/assessment visit.
- Table: for both weight and BMI, descriptive statistics of change from baseline by treatment group, total and by treatment/assessment visit.

Both weight and BMI will be listed by patient.

6.7 Physical Examination

The number and percentage of patients with abnormal physical examination findings will be presented for each body system by treatment group and total for each visit. Individual patient physical examination data will be listed for all enrolled patients.

Table 5 Physical Examination – Body System Examined

Cardiovascular / Circulatory
Digestive / Excretory
Endocrine
Integumentary / Exocrine
Lymphatic / Immune
Muscular
Nervous
Renal / Urinary
Reproductive
Respiratory
Skeletal

6.8 ECOG Performance Status

The number and percentage of patients in the categories of the ECOG performance status will be presented by treatment group and total for each visit. Individual patient ECOG performance status will be listed for all patients.

Table 6 ECOG Performance Status

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

6.9 Overall Response Rate (POLAR-M only)

Patients will be evaluated for response according to RECIST v1.1 guidelines. The overall response rate (ORR) is the best response (CR or PR) recorded during chemotherapy treatment. Overall response data is collected at treatment visits 5, 7, 9, end of treatment, and assessment visits month 3, 6, 9, 12 and 15.

The following categories of the overall response assessment will be recorded:

- CR = Complete Response
- PR = Partial Response
- SD = Stable Disease
- PD = Progressive Disease
- NE = Not Evaluable

Derived variables

Overall response rate (ORR) is defined as the best overall response (CR or PR).

Data presentations

- Table: overall response (OR) - number and percentage of patients by treatment group and treatment/assessment visit.
- Table: overall response rate (ORR) - number and percentage of patients by treatment group and treatment/assessment visit.

Overall response will be listed by patient.

6.10 Progression-Free Survival (POLAR-M only)

Endpoint. Progression-Free Survival (PFS) is defined as the time from the date of randomisation until the date of objectively determined PD (according to RECIST v1.1) or death due to any cause. Patients without objectively determined PD who are alive at the end of the follow-up period (or who were lost to follow up) will be censored on the date of the patient's last complete radiographic tumor assessment. If no baseline or post-baseline radiologic assessment is available, the patient will be censored at the date of randomisation.

Cox Proportional Hazards Model. Time (number of days) from randomisation to event or censoring will be analysed by a cox proportional hazards model using region (Asia / non-Asia) and Treatment as fixed factors in the model. The hazard ratio along with its 95% confidence interval of the PledOx doses compared to placebo will be estimated.

Data presentations

- Table: Progression-free survival based on the cox proportional hazards model will be presented by the number and percentage of events (N, %), Hazard Ratio (95% CI), Minimum, Q1, Median, Q3 and Maximum time to event or censoring by treatment group and total.
- Figure: Progression-free survival will be depicted graphically by a Kaplan-Meier plot by treatment group.

All PFS data will be listed by patient.

6.11 Overall Survival (POLAR-M only)

Endpoint. Overall Survival (OS) is defined as the time from the date of randomisation until the date of death from any cause. If the patient was alive at the end of the follow-up period (or was lost to follow-up), the patient will be censored on the last date the patient was known to be alive.

Cox Proportional Hazards Model. Time (number of days) from randomisation to event or censoring will be analysed by a cox proportional hazards model using region (Asia / non-Asia) and Treatment as fixed factors in the model. The hazard ratio along with its 95% confidence interval of the PledOx doses compared to placebo will be estimated.

Data presentations

- Table: Overall survival based on the cox proportional hazards model will be presented by the number and percentage of events (N, %), Hazard Ratio (95% CI), Minimum, Q1, Median, Q3 and Maximum time to event or censoring by treatment group and total.
- Figure: Overall survival will be depicted graphically by a Kaplan-Meier plot by treatment group.

All OS data will be listed by patient.

6.12 Disease-Free Survival (POLAR-A only)

Endpoint. Disease-Free Survival (DFS) is defined as the time from the date of randomisation until the date of objectively determined signs or symptoms of recurrence of Colorectal Cancer (CRC) or death due to any cause. Signs and symptoms may include any assessment result that, in the opinion of the Investigator, provides evidence for the recurrence of the disease. Patients without objectively determined disease recurrence who are alive at the end of the follow-up period (or who were lost to follow up) will be censored on the date of the patient's last assessment of disease recurrence. If no baseline or post-baseline radiologic assessment is available, the patient will be censored at the date of randomisation.

Cox Proportional Hazards Model. Time (number of days) from randomisation to event or censoring will be analysed by a cox proportional hazards model using region (Asia / non-Asia) and Treatment as fixed factors in the model. The hazard ratio along with its 95% confidence interval of PledOx 5 µmol/kg compared to placebo will be estimated.

Data presentations

- Table: Disease-free survival based on the cox proportional hazards model will be presented by the number and percentage of events (N, %), Hazard Ratio (95% CI), Minimum, Q1, Median, Q3 and Maximum time to event or censoring by treatment group and total.
- Figure: Disease-free survival will be depicted graphically by a Kaplan-Meier plot by treatment group.

All DFS data will be listed by patient.

7. REFERENCES

1. Breslow NE, Day NE (1987). The Design and Analysis of Cohort Studies. IARC Scientific Publications No. 82 Lyon, France, page 110.
2. Robins J, Breslow N, Greenland S (1986). Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. Biometrics 42:311-323.