CONFIDENTIAL

CLINICAL STUDY PROTOCOL

STUDY TITLE: A Phase 3, double-blind, multicenter, placebo-controlled study of PledOx used on top of modified FOLFOX6 (5-FU/FA and Oxaliplatin) to prevent chemotherapy induced peripheral neuropathy (CIPN) in the adjuvant treatment of patients with Stage III or high-risk Stage II colorectal cancer

SHORT TITLE: **P**reventive treatment of **O**xa**L**iplatin induced peripher**A**l neu**R**opathy in **A**djuvant colorectal cancer (**POLAR-A**)

PROTOCOL NUMBER: PP06489

EUDRACT NUMBER: 2017-004707-43

IND NUMBER: Not applicable

STUDY DRUG: PledOx

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VERSION TABLE

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STATEMENT OF CONFIDENTIALITY

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SIGNATURE PAGE

This study protocol was subjected to critical review. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

This protocol is approved by:

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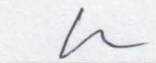
Coordinating Investigator Kei Muro, MD Aichi Cancer Center Hospital, Japan	 Signature	20 May, 2020 Date

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This Protocol has been written in accordance with current ICH-GCP guidelines.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5-FU	5-fluorouracil
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
β-HCG	β-human choriongonadotropin
CEA	Carcinoembryonic antigen
CI	Confidence interval
CIPN	Chemotherapy induced peripheral neuropathy
(m)CRC	(metastatic) Colorectal cancer
(N)CS	(Not) Clinically significant
CSR	Clinical study report
CT	Computer tomography
DFS	Disease free survival
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQol – 5 Dimensions – 5 Levels
FDA	Food and Drug Administration
FA	Folinic acid
FAS	Full analysis set
FACT/GOG-NTX-13	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity-13-item subscale
FSH	Follicle stimulating hormone
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factor
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board

i.v.	Intravenous
mFOLFOX6	Modified FA + 5-FU + oxaliplatin chemotherapy regimen
MedDRA	Medical Dictionary for Regulatory Activities
Mn	Manganese
MnDPDP	Mangafodipir
MnSOD	Manganese superoxide dismutase
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect-level
NRS	Numerical rating scale
OR	Odds ratio
PPS	Per protocol set
QA	Quality assurance
QoL	Quality of life
RBC	Red blood cell (count)
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SSC	Study Steering Committee
ULN	Upper limit of normal
WBC	White blood cell (count)
WOCBP	Women of child-bearing potential

2. PROTOCOL SYNOPSIS

Title (Full)	A Phase 3, double-blind, multicenter, placebo-controlled study of PledOx used on top of modified FOLFOX6 (5-FU/FA and Oxaliplatin) to prevent chemotherapy induced peripheral neuropathy (CIPN) in the adjuvant treatment of patients with Stage III or high-risk Stage II colorectal cancer
Title (Short)	**P**reventive treatment of **O**xa**L**iplatin induced peripher**A**l neu**R**opathy in **A**djuvant colorectal cancer (**POLAR-A**)
Protocol Number	PP06489
IND Number	Not applicable
EudraCT Number	2017-004707-43
Investigational Product	PledOx
Co-ordinating Investigator:	Camilla Qvortrup, MD, PhD The Finsen Center – Rigshospitalet, Department of Oncology Blegdamsvej 9 Copenhagen, DK-2100 Denmark Kei Muro, MD Director and Chief Department of Clinical Oncology Outpatient Treatment Center, Aichi Cancer Center Hospital 1-1 Kanokoden, Chikusa, Nagoya, Aichi 464-8681 Japan
Number of Sites and Countries	Approximately 95 centers in Europe and Asia
Phase	Phase 3
Indication	Prevention of chemotherapy induced peripheral neuropathy (CIPN)
Study Design	This is a Phase 3, multicenter, double-blind, placebo-controlled study with PledOx for prevention of chronic CIPN induced by oxaliplatin in patients with Stage III or high-risk Stage II colorectal cancer (CRC). Patients with CRC, who are indicated for adjuvant modified FOLFOX6 (mFOLFOX6) chemotherapy for up to 6 months, will be randomized in a 1:1 ratio to 1 of 2 treatment arms: • Arm A: PledOx (5 µmol/kg) + mFOLFOX6 chemotherapy • Arm B: Placebo + mFOLFOX6 chemotherapy Before March 2nd., 2020, the investigational medicinal product (IMP; i.e. PledOx or placebo) was administered by an intravenous (i.v.) infusion on the first day of each chemotherapy cycle. IMP was not to be administered if mFOLFOX6 was not given to the patient. If a patient discontinues oxaliplatin, treatment with 5-FU/folinate may be continued.

	As of March 2nd., all patients have to stop IMP but may continue mFOLFOX6.
Primary Objective	To compare PledOx (5 µmol/kg) vs placebo with respect to the proportion of patients with moderate or severe chronic CIPN.
Secondary Objectives	To compare 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> • Disease free survival (DFS) • Safety and tolerability
Exploratory Objectives	To compare 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 functional impairment (in the non-dominant hand) during long-term follow-up • The worst pain in hands or feet during long-term follow-up. • Quality of life (QoL)/health status • Health economic impact
Study Duration	Enrolment period: 16 months First patient in: October 2018 Last patient in: March 2nd., 2020 Treatment Phase: at least 12 weeks (3 months) up to 24 weeks (6 months) Follow-up Phase: 24 months after first dose of IMP Total study duration (from first dose of IMP to the End of Study): 24 months A data cut-off implementation date is estimated by 30 September 2020.
Principal Selection Criteria	<u>Inclusion criteria</u> 1. Signed informed consent form before any study related assessments and willing to follow all study procedures. 2. Male or female aged ≥18 years.

	3. Pathologically confirmed adenocarcinoma of the colon or rectum including: Stage III carcinoma (any T N1,2 M0) or Stage II carcinoma (T3,4 N0 M0). 4. The patient has undergone curative (R0) surgical resection performed within 12 weeks prior to randomization 5. The patient has a postsurgical carcinoembryonic antigen (CEA) level ≤1.5 x upper limit of normal (ULN, in current smokers, CEA level ≤2.0 x ULN is allowed). 6. No prior anti-cancer therapy for CRC except radiotherapy or concomitant chemo-radiotherapy using a fluoropyrimidine alone for locoregional rectal cancer. 7. Patient indicated for up to 6 months of oxaliplatin-based chemotherapy and without pathological findings of a neurologic exam performed prior to oxaliplatin treatment according to local practice. 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 9. Adequate hematological parameters: hemoglobin ≥100 g/L, absolute neutrophil count ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L. 10. Adequate renal function: creatinine clearance >50 cc/min using the Cockcroft and Gault formula or measured. 11. Adequate hepatic function: total bilirubin ≤1.5 x ULN (except in the case of known Gilbert's syndrome); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x ULN. 12. Baseline blood manganese (Mn) level <2.0 x ULN. 13. For patients with a history of diabetes mellitus, HbA1c ≤7%. 14. Negative pregnancy test for women of child-bearing potential (WOCBP). 15. For men and WOCBP, use of adequate contraception (oral contraceptives, intrauterine device or surgically sterile) while on study drug and for at least 6 months after completion of study therapy. <u>Exclusion criteria</u> 1. Any evidence of metastatic disease. 2. Any unresolved toxicity by National Cancer Institute-Common Terminology Criteria for Adverse Events Version (NCI-CTCAE) v.4.03 >Grade 1 from previous anti-cancer therapy (including radiotherapy), except alopecia. 3. Any grade of neuropathy from any cause. 4. Any evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, cardiac, unresolved bowel obstruction, hepatic or renal disease). 5. Chronic infection or uncontrolled serious illness causing immunodeficiency. Patients with known history of chronic hepatitis B can be enrolled if they are asymptomatic and an acute and active HBV infection can be excluded. 6. Any history of seizures 7. A surgical incision that is not healed. 8. Known hypersensitivity to any of the components of mFOLFOX6 and, if applicable, therapies to be used in

	conjunction with the chemotherapy regimen or any of the excipients of these products. 9. History of other malignancies (except for adequately treated basal or squamous cell carcinoma or carcinoma in situ) within 5 years, unless the patient has been disease free for that other malignancy for at least 2 years. 10. Known dihydropyrimidine dehydrogenase deficiency. 11. Pre-existing neurodegenerative disease (e.g., Parkinson's, Alzheimer's, Huntington's) or neuromuscular disorder (e.g., multiple sclerosis, amyotrophic lateral sclerosis, polio, hereditary neuromuscular disease). 12. Major psychiatric disorder (major depression, psychosis), alcohol and/or drug abuse. 13. Patients with a history of second or third degree atrioventricular block or a family heredity. 14. A history of a genetic or familial neuropathy. 15. Treatment with any investigational drug within 30 days prior to randomization. 16. Pregnancy, lactation or reluctance to using contraception. 17. Any other condition that, in the opinion of the Investigator, places the patient at undue risk. 18. Previous exposure to mangafodipir or calmangafodipir. 19. Welders, mine workers or other workers in occupations (current or past) where high Mn exposure is likely.
Study Drug Formulation, dosage, administration	PledOx (calmangafodipir, 50 mM i.v. solution) given as a single dose infused over approximately 10 minutes, 15 minutes prior to each mFOLFOX6 cycle. PledOx 5 µmol/kg i.v. dosed every 2 weeks and administered with mFOLFOX6 (Arm A).
Reference Therapy Formulation, dosage, administration	Placebo (0.9% NaCl), given as a single dose infused over approximately 10 minutes, 15 minutes prior to each mFOLFOX6 cycle (Arm B).
Background Anti-tumor Therapy (Chemotherapy) Formulation, dosage, administration	mFOLFOX6 (calcium-folinate or calcium-levofolinate, 5-FU and oxaliplatin) will be administered in 2-week cycles (Arms A and B) according to approved Summary of Product Characteristics.
Visit Schedule	There will be 2 types of study visits. Before March 2nd., 2020, at Treatment Visits, the patient received IMP on the first day of each mFOLFOX6 cycle. As of March 2nd, 2020, treatment visits will be done for patients receiving mFOLFOX6 on the first day of each cycle, without IMP, until Cycle 12. Assessment Visits will be performed every 3 months from the first dose of IMP, for up to 12 months, thereafter every 6 months, for up to 24 months.

	For further details see the Schedule of Assessments at the end of the synopsis and in Appendix 1.
Criteria for Evaluation	**Primary Endpoint** • 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). **Secondary Endpoints** <u>Efficacy</u> • 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 • 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 • Mean cumulative dose of oxaliplatin administered per patient during mFOLFOX6 chemotherapy, 9 months after the first dose of IMP • Mean change from baseline in vibration sense, on the lateral malleolus (left and right), using a graduated tuning fork, at 9 months after the first dose of IMP • 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 • Mean change from baseline in the time to complete the grooved Pegboard with the non-dominant hand, at 9 months after the first dose of IMP • 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, 18, and 24 months after the first dose of IMP <u>Safety</u> • DFS at 12 and 24 months • Safety and tolerability as assessed by adverse events (AEs), laboratory variables and vital signs • Proportion of patients with PledOx toxicities in addition to chemotherapy-related toxicities graded using the NCI-CTCAE v4.03 **Exploratory Endpoints** • 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

	• 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 • Mean score of the 13 items of the FACT/GOG-NTX-13, at 9 months after the first dose of IMP • Mean cumulative dose of 5-FU administered per patient during mFOLFOX6 chemotherapy, 9 months after the first dose of IMP • For both oxaliplatin and 5-FU: Dose intensity, mean number of cycles per patient, proportion of patients with any dose reduction, reason(s) for dose reductions, proportion of patients with any dose delay, and mean duration of dose delay • Mean health index and mean visual analogue scale (VAS) score, using the EQ-5D-5L, at 9, 12, 18, and 24 months after the first dose of IMP • Mean health index, using the FACT/GOG, at 9, 12, 18, and 24 months after the first dose of IMP • Mean time to complete the grooved Pegboard, with the non-dominant hand, at 12, 18, and 24 months after the first dose of IMP • Mean change from baseline in worst pain in hands or feet in the past week, using a NRS, at 12, 18, and 24 months after the first dose of IMP • The proportion of patients with a 2-point, 3-point and 4-point increase in worst pain in hands or feet in the past week, using a NRS, at 9, 12, 18, and 24 months after the first dose of IMP • 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, 12, 18 and 24 months after the first dose of IMP An independent Data Safety Monitoring Board (DSMB) will monitor accumulating safety, efficacy and other types of data throughout the study.
Study Populations	Four analysis populations will be defined: • All patients randomized will be included in the All Randomized Patients population, according to their randomized treatment • The intention to treat principle is used to define the primary analysis population, the Full Analysis Set (FAS), which will consist of all randomized patients who receive at least 1 dose of IMP • The Per Protocol Set is defined as a subset of the FAS constituted by patients who: (a) meet all inclusion/exclusion criteria liable to affect the efficacy assessment, and (b) do not present any major protocol deviations • The Safety Analysis Set will consist of all patients included in the study and treated with at least 1 dose of IMP
Statistical Methods	Following the premature study hold, the power of the study has been affected as a results of the premature stop of IMP dosing in individual patients. For that reason the statistical analyses will be done on the combined

	dataset of the POLAR-A and POLAR-M study, with data from POLAR-A and POLAR-M cohorts being evaluated as separate strata. For the details of the combined and stratified analyses, please refer to the SAP. Below the Statistical Methods can be found as originally described. The primary endpoint will be analyzed only once when patients have completed and reached 12 months. Analysis of primary endpoint, major secondary endpoints and current safety data will be performed after all patients have completed treatment and reached 12 and 24 months after first dose of IMP. In addition, survival data will be analyzed after 24 months. Final evaluation and analysis of study data will be performed after all patients have completed the study. The active arm will be statistically tested against placebo. For the test the statistical hypothesis is: H0: PledOx treatment arm is equal to placebo with respect to the primary efficacy endpoint. H1: PledOx treatment arm is not equal to placebo with respect to the primary efficacy endpoint. For the primary endpoint, the Cochran-Mantel-Haenszel test will test the following two-sided hypothesis: H0: $\Psi=1$ versus H1: $\Psi\neq1$ where Ψ defines the common odds ratio (OR) of PledOx to placebo across all strata. An OR<1 favors the PledOx group. The overall type I family-wise error rate for testing the primary and the main secondary efficacy endpoints will be controlled at the 0.05 significance level using a multiple comparison procedure. All hypothesis tests will be two-sided. The primary endpoint will be presented descriptively (n, %) together with its corresponding 95% confidence interval (CI) based on the Wilson-score method and will be presented for both treatment groups. The Cochran-Mantel-Haenszel test will be performed as an analysis using the baseline score of FACT/GOG (2 levels), treatment and region. The OR, 95% CI and p-value using the Cochran-Mantel-Haenszel test for the difference in event rates between the 2 treatment groups will be presented. The results from the Cochran-Mantel-Haenszel test are considered the primary analysis results using the FAS. Other secondary endpoints will be using two-sided hypothesis testing and details will be presented in the Statistical Analysis Plan. All tests will be two-sided and a pre-defined hierarchical family wise test order will be used to control the 0.05 type-I error rate.
Sample Size	Assumptions with regards to the revised samples size following the premature hold of the study are described in the final SAP. 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 randomized.

	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.

Schedule of Assessments (short version)

POLAR-A	SELECTION PHASE				TREATMENT PHASE													EOT[13]		FOLLOW-UP PHASE[14]			
					+/- 2 days													D 14 of last cycle +/- 3 days		+/- 1 week			
Visits in **Month**												M3							M6[11]	M9	M12	M18	M24
Visit in **Days** per **Cycle**	D-28	D-14	D-7	D0	D1C1	D1C2	D1C3	D1C4	D1C5	D1C6	D1C7		D1C8	D1C9	D1C10	D1C11	D1C12	D14C12					EOS
Visits in **Weeks**	W-4		W-1	not a visit	W0	W2	W4	W6	W8	W10	W12		W14	W16	W18	W20	W22	W24					
Informed Consent	x																						
Demography, Prior Medication (including D-30 medication)			x																				
Medical History			x																				
Screening ECG (QTc)			x																				
Inclusion/Exclusion Criteria, Randomization[6]				x																			
CT/MRI scan and Disease assessment[1]	x																				x		x
Disease Free Survival												x							x	x	x	x	x
CarcinoEmbryonic Ag (CEA)			x															x			x		x
Vital signs (T°, pulse rate, BP) and weight (except after EOT)			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test (serum)[2]			x	results	x		x		x		x			x		x		x					
Hematology[3]			x	results	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Biochemistry[4]			x	results	x		x		x		x			x		x		x					
Manganese blood sample[5]	x			results				x					x				x	x					
ECOG Performance Status			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Grooved PEG-board & Vibration Sensitivity Testing					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FACT/GOG-NTX-13[7]					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pain Numeric Rating Scale (NRS)[7]					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
QoL (EQ-5D-5L)[7]					x			x				x	x				x	x	x	x	x	x	x
Cold Sensitivity Diary (pre-dose, post dose of D1 + D2 and D3)			x			x		x					x										
PledOx/Placebo Infusion (before mFOLFOX)[8]					x	x	x	x	x	x	x		x	x	x	x	x						
Physical examination			x									x						x	x	x	x	x	x
Brain MRI and Blood Mn incl. neurological exam [10]					(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)					
Concomitant Medication[9]					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Adverse Events[9]					x	x	x	x	x	x	x		x	x	x	x	x	x					
Health Economics Impact[12]					x														x		x	x	x

AE = adverse event; BP = blood pressure; CEA = Carcinoembryonic antigen; CT = computed tomography; D = day; DFS = disease free survival; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoS = end of study; EoT = end of treatment; FACT/GOG-NTX-13 = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity-13-item subscale; M = month; Mn = manganese; MRI = magnetic resonance imaging; NRS = numeric rating scale; QoL = quality of life; T = temperature; W = week

[1] CT-scan or MRI, but the same assessment should be performed throughout the study for each patient. For screening, results from a scan performed within 42 days prior to surgery or after surgery are allowed. Tumors will be analyzed and records will be evaluated locally.

[2] WOCBP must give a negative serum pregnancy test at screening and then every 4 weeks while patient is on IMP treatment

[3] Hematology (every Treatment Visit): WBC count differential, ANC, RBC count, platelet count, and hemoglobin. Analyzed by a local hospital laboratory.

[4] Biochemistry (every 4 weeks or every 2nd Treatment Visit): ALP, total bilirubin, ALT, AST, serum creatinine, and albumin. Analyzed by a local hospital laboratory.

[5] Blood Mn (full blood): Collected at Day -28 Visit, Treatment Visit 4, 8, 12 and EOT. A patient can be enrolled without the result of Mn level analysis before the randomization, but the result should be confirmed prior to Cycle 1 Day 1. Mn samples will also be taken whenever Parkinson-like symptoms occur. Analyzed by a central laboratory.
As of March 2nd., 2020, no more Blood Mn samples will be taken with the exception for patients with Parkison-like symptoms.

[6] Randomization (within 3 days prior to Cycle 1 Day 1)– this is not a patient visit. This is the moment when the Investigator will confirm that a patient complies with all inclusion/exclusion criteria and the patient will be randomized into a treatment arm using the electronic randomization system within the eCRF. The Investigator will then request the unblinded pharmacist/designee to prepare the study treatment according to the randomization schedule available only to the unblinded hospital staff.

[7] Questionnaire to be completed by the patient in the hospital.
During the COVID-19 pandemic, remote data collection via either phone call or mailing of paper copies of rating scales for completion at home may be implemented.

[8] IMP (PledOx or placebo) will be administered before the background chemotherapy (mFOLFOX6). Study treatment will be stopped in case of mFOLFOX6 treatment discontinuation, disease progression, intolerable toxicity or withdrawal of consent.
As of March 2nd., 2020, the IMP administration is stopped in ongoing patients and no new patients are included in the study.

[9] All AEs including SAEs and concomitant medications will be collected up to 30 days after the last administration of IMP. AEs will be followed until resolution.
As of March 2nd., 2020, all AEs including SAEs and concomitant medications will be collected up to 30 days after the EOT visit and followed until resolution.

[10] In patients who develop Parkinson-like symptoms, a neurological examination and a brain MRI will be performed and an additional blood Mn sample will be analyzed. A brain MRI should also be performed if elevated Mn is found during the scheduled Mn samples.

[11] If the patient continues with the study treatment until Treatment Visit 12 (Week 22), the relevant Treatment Visit or the End of Treatment Visit will be combined with the Assessment visit at Month 6. The Assessment visit at Month 6 will be performed as a separate visit only if a patient stops study treatment prior to Treatment Visit 12 (Week 22).
As of March 2nd., 2020, if the patient continues with mFOLFOX6 without IMP until Treatment Visit 12 (Week 22), the relevant Treatment Visit or the End of Treatment Visit will be combined with the Assessment Visit at Month 6. The Assessment Visit at Month 6 will be performed as a separate visit only if a patient stops mFOLFOX6 prior to Treatment Visit 12 (Week 22)

[12] The Health Economic Impact Questionnaire will be completed by the Investigator or well-trained site staff. During the COVID-19 pandemic the Health Economic Impact Questionnaire can be done via phone or by mailing paper copies for completion at home if a site visit is not possible and.

[13] At time of estimated data cut-off date by 30 September 2020, all patients who are still in the Treatment Phase have an EOT visit on Day 14 ± 3 days of the last cycle with mFOLFOX6 before the data cut-off date.

[14] During the COVID-19 pandemic, a visit window of ± 6 weeks is allowed during the Follow-up Phase.

3. BACKGROUND INFORMATION

3.1 COLORECTAL CANCER

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and is the third leading cause of cancer death (Siegel et al. 2017). Fundamentally CRC is a genetically and clinically heterogeneous disease. The evolving understanding of the molecular aberrations (e.g., microsatellite instability) and clinical factors (e.g., right-sided or left-sided localization of the primary tumor) is hoped to impact the therapeutic paradigm of the future (Boisen et al. 2013; Brule et al. 2015; Guinney et al. 2015; Moretto et al. 2016; Dienstmann et al. 2017; Tejpar et al. 2017).

Fortunately, approximately 80% of the patients present with resectable disease that can be potentially cured with appropriate therapy. Adjuvant chemotherapy for Stage III CRC is now widely accepted as it decreases the relapse rate and improves disease free survival (DFS) compared to surgery alone. The benefit of adjuvant chemotherapy in Stage II is more limited and remains controversial, and, if used, it is generally reserved for tumors with high-risk features (McCleary et al. 2017).

3.2 PERIPHERAL NEUROPATHY INDUCED BY OXALIPLATIN

Oxaliplatin, a third-generation cisplatin analogue, is approved in combination with infusional 5-FU/FA (5-fluorouracil/folinic acid; FOLFOX) for the treatment of metastatic as well as adjuvant as CRC (Alcindor et al. 2011). Despite its success, a number of key safety issues place limitations on the potential efficacy of this agent, particularly neurotoxicity.

Oxaliplatin induces 2 distinct forms of chemotherapy-induced peripheral neuropathy (CIPN) that are thought to arise by different mechanisms (Weickhardt et al. 2011). The first is a very common and pathognomonic acute syndrome (Wilson et al. 2002) that is transient and appears during, or shortly after, exposure to oxaliplatin, and a dose-limiting chronic sensory neurotoxicity that is cumulative (Sereno et al. 2014).

Acute peripheral neuropathy is observed in >90% of patients exposed to FOLFOX-4 (Andre et al. 2004). It consists of sensory symptoms in the fingertips and toes in a “stocking and glove” distribution, which are classically triggered by exposure to cold. Perioral numbness, jaw spasms and muscle cramps can also be seen. Although acute symptoms can be disturbing for patients, this symptom complex is transient and usually (Lehky et al. 2004; Wilson et al. 2002) but not always (Pachman et al. 2015) reversible. The pathogenesis of acute oxaliplatin-induced neuropathy is thought to be due to a disturbance of axonal sodium channels by the oxalate salt of oxaliplatin (Adelsberger 2000; Gamelin et al. 2007).

By contrast, oxaliplatin-induced chronic neurotoxicity is related to the cumulative dose of oxaliplatin administered over time and is not cold-triggered, and the pathogenesis is similar to the neuropathy caused by other platins (Weickhardt et al. 2011; Zimmerman et al. 2016, and references therein). It can be dose-limiting, and the symptoms may last for years and severely impact quality of life (QoL) (Driessen et al. 2012; Tofthagen et al. 2012). Symptoms include numbness and tingling, affects hands and feet, and includes burning and shooting pain symptoms. Sensory impairment of peripheral neural function can lead to impairment of activities of daily living, such as writing and buttoning. Physiologic and pathologic studies reveal chronic morphologic damage and reduced sensory conduction velocity. These changes

become apparent at greater cumulative doses of oxaliplatin, particularly above a cumulative dose of 410 mg/m^2 (Loprinzi et al. 2014, and references therein). The symptoms may continue to worsen at higher doses. Specifically, the incidence of severe adverse events (AEs) is approximately 15% after a cumulative dose of 780 to 850 mg/m^2 and 50% after a cumulative dose of 1170 mg/m^2. Also, in what is referred to as the "coasting" phenomenon," in 10-15% of patients the symptoms of peripheral sensory neurotoxicity emerge or worsen a period after the completion of oxaliplatin therapy (Andre et al. 2004; Loprinzi et al. 2014).

The pathogenesis of chronic neurotoxicity may be due to mitochondrial dysfunction and deficient adenosine triphosphate production (Bennett et al. 2014, and references therein). Abnormally vacuolated mitochondria in peripheral nerve sensory axons can be seen in preclinical models after oxaliplatin exposure and induction of painful peripheral neuropathy (Zheng 2011). Axonal excitability studies also demonstrate ongoing and progressive changes in peripheral nerve function (Zheng et al. 2011). A preventative and therapeutic role for antioxidants has been demonstrated in some studies (Cascinu et al. 2002; Lin et al. 2006). After oxaliplatin induced painful neuropathy, peripheral nerves also contain significantly elevated levels of nitrated manganese superoxide dismutase (MnSOD), a key mitochondrion-specific antioxidant enzyme. As a result, MnSOD activity is greatly reduced. Treatment with a superoxide dismutase mimetic prevents and reverses both acute and chronic oxaliplatin-induced neuropathies as well as the mitochondrial deficit. The most compelling demonstration in clinic so far has been with the use of a MnSOD mimetic, mangafodipir (Coriat et al. 2014) and calmangafodipir (Glimelius et al. 2017).

Taken together, despite some studies demonstrating amelioration of oxaliplatin-induced CIPN, it is generally accepted that no pharmacologic agent has shown definitively to prevent CIPN (Pachman et al. 2014). Although duloxetine, a nonopioid, has been shown to be effective in the amelioration of neuropathic pain, to date the clinical experience has not validated the data from the trial (Hershman et al. 2014; Loprinzi et al. 2014; Majithia et al. 2016).

In the absence of effective pharmacologic interventions, a number of trials have examined the duration of oxaliplatin exposure and stop-and-go strategies in the metastatic setting in an attempt to reduce the incidence or severity of CIPN (Tournigand et al. 2006; Maindrault-Goebel et al. 2007).

This strategy has also been evaluated in the adjuvant setting, and the most recent and complete development was the data from the IDEA collaboration (Shi et al. 2017), which described the combined experience from 6 large adjuvant trials and 12,834 patients. The trial evaluated the concept that 3 months of oxaliplatin-based chemotherapy is non-inferior to 6 months of therapy with regard to DFS but advantageous with regard to CIPN. The trial failed to meet its primary endpoint of demonstrating non-inferiority for the 3-month duration of therapy. However, additional analyses revealed 3 months of adjuvant chemotherapy with capecitabine and oxaliplatin-based regimen was noninferior to 6 months for patients with high-risk Stage II or Stage III colon or rectal cancer, but this secondary finding was not noted with FOLFOX. Therefore, although there may be clinical strategies to manage CIPN, overall CIPN remains an unmet medical need particularly with regard to any pharmacologic therapy.

3.3 Name and Description of the Investigational Product(s)

PledOx®

Details of PledOx mechanism of action, preclinical and available clinical data are described in the Investigator Brochure.

PledOx (calmangafodipir; $Ca_4Mn(DPDP)_5$) mimics the activity of the MnSOD, and thereby helps to degrade reactive oxygen species and allows cells to survive oxidative stress. PledOx is a stabilized version of mangafodipir (MnDPDP), which was approved by the Food and Drug Administration (FDA) and European Health Authorities in 1997 for use in patients as a contrast agent for magnetic resonance imaging (MRI) of the liver and pancreas. Experience with mangafodipir as a contrast agent from more than 240,000 patients reveals a good safety and tolerability profile after a single administration. Mangafodipir marketing was later discontinued for commercial reasons (Karlsson et al. 2015).

PledOx is a potentially more potent and safer form of mangafodipir. It has shown promising activities in model systems in preventing oxaliplatin-induced adverse effects (Karlsson et al. 2012). Mn^{2+} is dissociated from the complexed drug after administration of both mangafodipir and PledOx. Although Mn^{2+} is considered essential, chronic exposure to Mn^{2+} could cause Parkinson like symptoms resulting from its accumulation in the brain (Guilarte 2010). In PledOx, 4 of 5 of the Mn^{2+} ions present in mangafodipir are replaced by more readily displaceable calcium (Ca^{2+}) ions, which stabilize the release of Mn^{2+} after administration resulting in a doubling of the renal excretion of fodipir bound Mn^{2+} (Karlsson et al. 2012). As an improved version of mangafodipir, PledOx is considered to have a lower risk due to the lesser amounts of free Mn^{2+}. In addition, at equivalent Mn^{2+} doses, PledOx was at least 10 times more potent than mangafodipir (Karlsson et al. 2012).

3.4 NON-CLINICAL FINDINGS

Results from pharmacology studies show that calmangafodipir protects BALB/c mice against the myelosuppressive effects of oxaliplatin and that the analogue mangafodipir effectively prevents the onset of locomotor and sensory disturbances as well as neuromuscular hyperexcitability in C57Bl/6 mice treated with oxaliplatin. Importantly, calmangafodipir does not interfere negatively with the antitumor activity of oxaliplatin; on the contrary, preclinical data suggest that it increases the antitumor efficacy in immune competent mice which might be an inherent property of DPDP or its dephosphorylated counterparts.

The general toxicity program with calmangafodipir consists of pilot repeat dose studies of 28 days duration in rats and dogs and clinical trial enabling 13-week studies in the same species as well as a 6 months study in rats and a 9 months study in dogs. The 28-day and 13-weeks studies used a dosage regimen of three injections per week rather than the once fortnightly regimen used in humans. The 6 and 9 months studies used the clinical regimen of once every fortnight.

Overall, the rat 13-week study revealed no toxicities of significant clinical concern in spite of single dose levels of calmangafodipir being up to 12-fold higher than the highest proposed clinical dose (5 µmol/kg) and 72-fold higher based on a fortnightly dose both calculated on a mg/m^2 basis. Calmangafodipir-related findings were restricted to apparent weight reductions of the testes and epididymides in high dose animals and lower pituitary weights in all male treated animals and in high dose females. The good tolerability observed in the 13-week study was confirmed in the 6 months study where the no-observed-adverse-effect-level (NOAEL) was the highest dose investigated; 1440 µmol/kg (1066.6 mg/kg body weight). This NOAEL is 46-fold the clinical dose on a mg/m^2 basis. Exposure measurement in terms of whole blood

Mn levels as well as C_{max} and $AUC_{0\text{-}inf}$ PLED give additional reassurance of good tolerability relative to the corresponding clinical exposures.

The dog 13-week study also did not reveal any toxicities of significant clinical concern in spite of single dose levels of calmangafodipir being 34-fold higher than the highest clinical dose (5 µmol/kg) on a mg/m^2 basis and 204-fold the cumulative dose over the clinical dosing interval of 14 days. The treatment could possibly have affected estrus cycling but owing to the low age of the animals the relationship of this to the treatment is uncertain. One high dose calmangafodipir animal showed testicular tubular atrophy. In addition to this, all animals showed various injections site reactions with a possibly higher incidence of hemorrhage in treated animals than in the controls, a finding of questionable clinical relevance in view of the absence of any calmangafodipir related injection site reactions in the 9 months dog study. This study showed vomiting and salivation in high dose animals of both sexes, lowered food consumption in high dose males and one early sacrifice of a high dose male owing to poor clinical condition. The NOAEL was the mid high dose, a dose being 33-fold higher than the clinical dose on a mg/m^2 basis. Results from exposure measurement (whole blood Mn levels as well as C_{max} and $AUC_{0\text{-}inf}$ PLED) relative to that in man, provide reassurance of good tolerability of calmangafodipir in the dog.

Fertility studies in male rats and embryofetal development studies in rats and rabbits have been conducted with mangafodipir. Skeletal malformations were observed in the embryofetal development study in rats at the lowest dose investigated and embryofetal toxicity was observed in rabbits. Identical effects were seen after administration of equimolar $MnCl_2$. It is the Sponsor's opinion that mangafodipir and calmangafodipir should have a similar reproduction toxicity liability.

Calmangafodipir was investigated for in vitro genotoxicity using the Ames Salmonella Assay and a micronucleus assay in human lymphocytes. No mutagenic activity was recorded. In the in vitro micronucleus assay with an extended 24 + 24 hour treatment at a cytotoxic dose (reduction in replication index of 66%), a weak induction of micronuclei was observed. The effect observed at such a high cytotoxic concentration is of questionable biological relevance. When the clastogenic activity of calmangafodipir was examined in a rat bone marrow micronucleus study in rats, no such activity was observed when after the administration of up to 2000 mg/kg (the regulatory maximum dose) on two consecutive days and bone marrow sampling 24 hours after the last dose.

3.5 CLINICAL FINDINGS

Oxaliplatin causes disabling acute and chronic peripheral neuropathy. We explored the preventive effects of calmangafodipir, mimicking the mitochondrial enzyme Mn superoxide dismutase, thereby protecting cells from oxidative stress, in a placebo-controlled, double-blinded randomized Phase 2 study (ClinicalTrials.gov, NCT01619423) in patients with metastatic colorectal cancer (mCRC).

mCRC patients treated with mFOLFOX6 (FA 200 mg/m^2, 5-FU bolus 400 mg/m^2, oxaliplatin 85 mg/m^2 and 5-FU 2400 mg/m^2 continuous infusion for 46 hours) every fortnight for 8 cycles in first or second line were eligible. Calmangafodipir was given in a Phase 1 dose-finding (Part 1) and in a Phase 2 placebo-controlled part of the study (Part 2 and 3), as a 5 minutes infusion, 10 minutes prior to oxaliplatin. Neurotoxicity was evaluated by the physician using the Oxaliplatin Sanofi Specific Scale and by the patient using the cold allodynia test (Ventzel

cylinder [Ventzel et al. 2016]) and the Leonard scale (oxaliplatin-associated neuropathy questionnaire, OANQ [Leonard et al. 2005]).

Eleven patients were included in Phase 1 without any detectable toxicity to calmangafodipir. In the Phase 2 study, 173 patients were randomized to placebo (n=60), calmangafodipir 2 µmol/kg (n=57) and calmangafodipir 5 µmol/kg (n=45, (part 2b) initially 10 µmol/kg, n=11 (part 2a). Calmangafodipir-treated patients (all 3 doses pooled) had less physician graded neurotoxicity (odds ratio [OR] (90% confidence interval [CI] one-sided upper level) 0.615 (1.159), p=0.158), less problems with cold allodynia and fewer sensory symptoms in the Leonard scale during treatment and during follow-up 3 and 6 months after last dose. Response rate, progression-free and overall survival did not differ among groups.

Calmangafodipir at a dose of 5 µmol/kg appears to prevent the development of oxaliplatin-induced acute and delayed CIPN without apparent influence on tumor outcomes.

SUNCIST a randomized, double-blind, placebo-controlled, ascending (2, 5 and 10 µmol/kg vs placebo, sequential enrolling cohort, single-dose study in healthy Japanese and Caucasian men, age 20 to 55 years, inclusive. 48 participants (24 Japanese and 24 Caucasian) were studied in two groups of three sequentially enrolling dose cohorts. Group 1 consisted of three cohorts of 8 Japanese subjects each, and Group 2 consisted of 3 cohorts of 8 Caucasian subjects each. Calmangafodipir at doses up to 10 µmoL/kg was safe and well tolerated. Calmangafodipir exposure ($AUC_{0\text{-last}}$ and C_{max}) was comparable for the Japanese and Caucasian subjects. $AUC_{0\text{-last}}$ and C_{max} increased proportionately with increasing dose.

In the adjuvant setting, the multicenter, international MOSAIC study was the first of several large trials to demonstrate a definitive role for oxaliplatin in the adjuvant setting (Andre et al. 2004, Andre et al. 2009). The study compared oxalipatin in combination with 5-FU/FA (FOLFOX-4) with the same 5-FU/FA regimen alone in 2446 patients with Stage II and III CRC (40% of the patients had Stage II and 60% had Stage III disease). The combination of oxaliplatin with 5-FU/FA was associated with statistically significant advantages over 5-FU/FA alone in terms of 3-year (72.2% versus 65.3%) and 4-year (69.7% versus 61%) survival rates in Stage III disease, but not in Stage II disease (3 years: 87.0% versus 84.3%; 4 years: 85.1% versus 81.3%). In a final analysis, the 6-year survival rates in patients with Stage III disease were 72.9% for FOLFOX-4 and 68.3% for 5-FU/FA alone (hazard ratio [HR] = 0.80). Among patients with stage II disease, no difference was observed between treatment groups in terms of 6-year survival rate (86.8%, HR = 1.00). However, the safety analysis demonstrated a number of toxicities that were significantly increased with the addition of oxaliplatin, including Grade 3 and 4 neutropenia (41% versus 4.7%), diarrhea (10.8% versus 6.6%), and allergic reactions (2.9% versus 0.2%). Paresthesia as a component of peripheral neuropathy was observed in 92% of patients in the FOLFOX-4 arm and in 15.6% of patients in the 5-FU/FA arm, while the frequencies of Grade 3 events in these arms were 12.4% and 0.2%, respectively.

Based on the results of this and subsequent large trials, FOLFOX or its variants containing oxaliplatin can be considered standard for the adjuvant therapy of patients with potentially curatively resected Stage III CRC. Moreover, 2- or 3-year DFS has also been shown to be highly predictive of overall survival at 5 and 6 years in Stage III patients (Sargent et al. 2011). Although not definitive, these data may not necessarily apply to selected high-risk Stage II patients; nevertheless, in many settings oxaliplatin is utilized for these patients.

3.6 POTENTIAL RISKS AND BENEFITS

Oxaliplatin-induced neuropathy is a serious condition with patients experiencing loss of QoL and the possibility of long-term neuropathic disabilities. Due to oxaliplatin-induced neuropathy, chemotherapy treatment may have to be reduced, postponed, or completely discontinued. This can lead to suboptimal treatment results and decreased survival in patients.

There are currently no existing/available therapies for the prevention of oxaliplatin-induced neuropathy. Calcium and magnesium infusions and neuromodulatory agents have been used and tested for prevention, however these agents have not proven to be sufficiently effective to become standard preventative agents for acute and chronic neuropathy.

The clinical evidence from the PLIANT (randomized controlled, Phase 2 study in patients with advanced or mCRC, n=173) provides evidence that PledOx can prevent CIPN during and after treatment with a commonly used oxaliplatin combination for patients with mCRC.

PledOx has demonstrated substantial improvement on clinically significant endpoints of neuropathy. Most notably, patients receiving PledOx were less likely to experience a Grade 2 or higher AE related to oxaliplatin-induced neuropathy in the PLIANT study. In addition, PledOx was shown to decrease patients' hypersensitivity to cold.

Overall, PledOx was very well tolerated. The frequency and severity of AEs for patients treated with PledOx was similar to patients treated with placebo. Additionally, the incidence of serious AEs (SAEs) was similar between the PledOx and placebo treated groups. There was only 1 SAE related to PledOx (hypersensitivity reaction with the 10 µmol/kg dose).

In conclusion, the CIPN effects are sufficiently strong and the lack of any indications of a tumor protective effect reassuring, motivating initiation of this Phase 3 study.

There are currently 2 ongoing studies with the study drug PledOx, this study and another study POLAR-M (adjuvant CRC setting). In the POLAR-A and POLAR-M studies, up to 19 December 2019, 125 SAEs were reported in patients treated with IMP.

One patient in the POLAR-M study had a hyperkalemia, which was considered 'Possibly Related' to the IMP by the Investigator.

Three patients in the POLAR-A program have been reported having had anaphylactoid reactions or allergic infusion reactions:

- One patient had an anaphylactoid reaction to the IMP during infusion. The IMP was probably the causative factor of the event.
- Two patients in the POLAR-A study had allergic infusion reactions/hypersensitivity; 1 patient had 2 events, both deemed 'Probably Related' by the Investigator, and the other patient's event was deemed as 'Possibly Related'.

As reported in these 3 patients, hypersensitivity reactions (urticaria and other possible allergic phenomena) or anaphylactoid reactions may occur, rarely. Familiarity with the practice and technique of resuscitation and treatment of anaphylaxis is essential. Appropriate medicinal products and instruments should be readily available (Roselló et al. 2017).

Two patients who were treated with the IMP have been reported seizures. One patient in the POLAR-A study had a 'tonic clonic seizure' of unknown origin with a fatal outcome, which was considered 'Possibly Related' to the IMP. The other patient, in the POLAR-M Study, had a seizure that was reported 2 days after IMP infusion. The event was considered to be unrelated to the IMP.

In a previous study sponsored by Pled Pharma, 'The PP100-01 for Overdose of Paracetamol Trial (POP Trial)', a female subject suffered from epilepsy and experienced 2 seizures, 2 days after treatment with N-Acetyl Cysteine and calmangafodipir after an overdose with paracetamol (acetoaminophen). The subject had missed 2 doses of anti-epileptic drug treatment, which was considered to be the causative factor of the seizures.The risk of Mn toxicity is low, precautions that further minimizes the risk that this will happen in individual patients are described in the protocol. They are among others that patients that develop Parkinson's-like symptoms, will be evaluated for elevated blood Mn levels.

On March 2nd., 2020, PledPharma and Solasia decided to put dosing and recruitment of patients in the POLAR-A study globally on hold, which was communicated to the study sites via a Dear Dr Letter dated March 2nd., 2020 and confirmed in a second DDL dated April 8th., 2020.
This decision followed a clinical hold of the POLAR-M study in the US issued by the FDA on January 22nd., 2020, and a similar request to stop recruitment and dosing of patients in the POLAR-A and POLAR-M studies in France made by the French Authority, ANSM.
Finally the Independent Data and Safety Monitoring Board (DSMB), following their review of unblinded safety data during their meeting in February and March 2020, recommended to stop both trials due to an accumulation of allergic reactions in the studies.
At that time 591 patients out of the planned 700 patients had been randomized, and 420 patients had completed more than 6 cycles of study drug treatment while 250 patients had completed more than 9 cycles.
In order to allow for the benefit-risk analysis to be based on as many patients as possible reaching their 9 month visit, PledPharma and Solasia in their DDLs have requested to make all necessary efforts collecting key efficacy and safety data in the POLAR studies up to the estimated data cut-off date by 30 September 2020.
The estimated data cut-off date by 30 September 2020 was selected so all patients eligible for 6 cycles of treatment with study drug have completed the 9-month data collection of the primary endpoint.

Finally, due to the COVID-19 situation and site/country restrictions, on April 2nd.,2020, a recommendation was made to allow remote data collection according to local requirements. In order to follow up and maintain patient safety and collect study-related data, the physical site visit of the patient may be replaced by a phone call or by mailing of paper copies of questionnaires for completion at the home of the patient.

3.7 TREATMENT

To date, approximately 420 patients with CRC have received repetitive dosing with PledOx.

3.8 CONDUCT OF STUDY

This clinical study will be conducted in compliance to this Protocol, the guidelines of the World Medical Association Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), designated standard operating procedures (SOPs), and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

3.9 POPULATION

The target population for this study is patients with pathologically confirmed CRC including Stage III carcinoma (any T N1,2 M0) or Stage II carcinoma (T3,4 N0 M0). Patient must have undergone curative surgical treatment, generally within 12 weeks prior to randomization.

Approximately 280 patients will be enrolled. The planned population of 280 patients will be enrolled at approximately 95 study centers.

There will be no additional patients included in order to compensate for withdrawals.

4. STUDY OBJECTIVES AND PURPOSE

4.1 OBJECTIVES

4.1.1 Primary Objective

- To compare PledOx (5 µmol/kg) vs placebo with respect to the proportion of patients with moderate or severe chronic CIPN

4.1.2 Secondary Objectives

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

4.1.3 Exploratory Objectives

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

4.2 RATIONALE

There are currently no effective preventive or therapeutic treatments for CIPN. Several agents have been tested, but all have failed to demonstrate a convincing benefit. The American Society of Clinical Oncology has recognized this limitation but made a moderate recommendation for duloxetine for the treatment of existing CIPN (Hershman et al. 2014). No pharmacologic intervention can be recommended for the prevention of CIPN.

The suggested dose of 5 µmol/kg has sufficient support in the PLIANT data. The 5 µmol/kg dose is the preferred dose based on available data, with an OR = 0.12 (p=0.018) vs placebo on the variable most like the primary endpoint in the POLAR studies (i.e., percentage of patients

with patient-reported Leonard scoring 3 or more on either numbness, tingling or burning pain/discomfort with cold at FU2, which is approximately 10 months after first dose).

Overall, it can therefore be concluded that there is a clear unmet medical need for the prevention of CIPN, and the PLIANT data justifies a confirmatory study of PledOx in this setting.

5. INVESTIGATIONAL PLAN

5.1 ENDPOINTS

5.1.1 Primary Endpoint

- 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 investigational medicinal product (IMP; i.e. PledOx or placebo administered on Day 1, Cycle 1 of mFOLFOX6 chemotherapy)

5.1.2 Secondary Endpoints

Efficacy

- 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
- 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
- Mean cumulative dose of oxaliplatin administered per patient during mFOLFOX6 chemotherapy, 9 months after the first dose of IMP
- Mean change from baseline in vibration sense, on the lateral malleolus (left and right), using a graduated tuning fork, at 9 months after the first dose of IMP
- 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
- Mean change from baseline in the time to complete the grooved Pegboard with the non-dominant hand, at 9 months after the first dose of IMP
- 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, 18, and 24 months after the first dose of IMP

Safety

- DFS at 12 and 24 months
- Safety and tolerability as assessed by AEs, laboratory variables and vital signs
- Proportion of patients with PledOX toxicities in addition to chemotherapy-related toxicities graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03

5.1.3 Exploratory Endpoints

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

- Mean cumulative dose of 5-FU administered per patient during mFOLFOX6 chemotherapy, 9 months after the first dose of IMP
- For both oxaliplatin and 5-FU: Dose intensity, mean number of cycles per patient, proportion of patients with any dose reduction, reason(s) for dose reductions, proportion of patients with any dose delay, and mean duration of dose delay
- Mean health index and mean VAS score, using the EQ-5D-5L, at 9, 12, 18, and 24 months after the first dose of IMP
- Mean health index, using the FACT/GOG, at 9, 12, 18, and 24 months after the first dose of IMP
- Mean time to complete the grooved Pegboard, with the non-dominant hand, at 12, 18, and 24 months after the first dose of IMP
- Mean change from baseline in worst pain in hands or feet in the past week, using a NRS, at 12, 18, and 24 months after the first dose of IMP
- The proportion of patients with a 2-point, 3-point and 4-point increase in worst pain in hands or feet in the past week, using a NRS, at 9, 12, 18, and 24 months after the first dose of IMP
- 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, 12, 18 and 24 months after the first dose of IMP

5.2 OVERALL STUDY DESIGN AND PLAN

This 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.

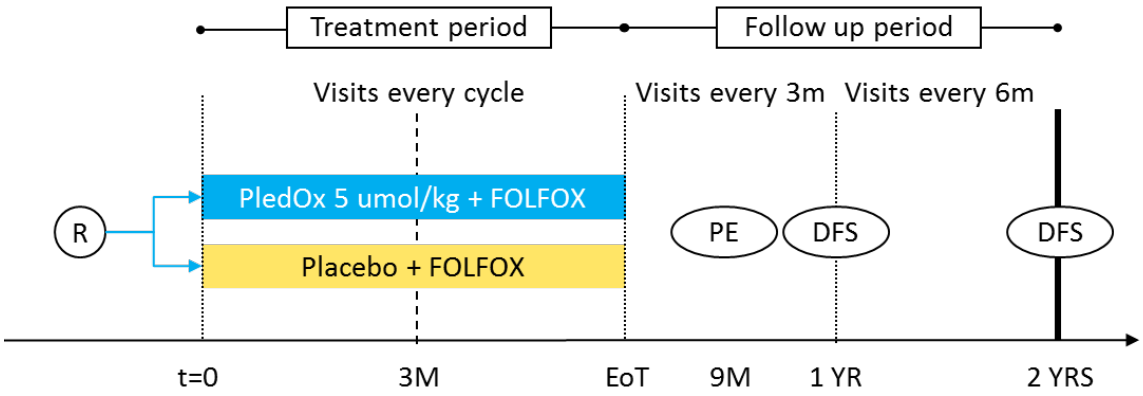
Patients will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

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

There will be 2 types of study visits:

- **Treatment Visits:** Before March 2nd., 2020, Visits occurred on the first day of each mFOLFOX6 cycle when the patient received IMP.
  As of March 2nd., 2020, treatment visits will be done for patients receiving mFOLFOX6 on the first day of each cycle, without IMP, until Cycle 12.
- **Assessment Visits:** Visits will be performed every 3 months from the first dose of IMP, for up to 12 months and thereafter every 6 months for up to 24 months.

Figure 1 Polar-A Study Design (As of March 2nd., 2020, no more IMP will be given)



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

Treatment Phase

Before March 2nd., 2020, patients were treated with IMP (i.e. PledOx or placebo) on top of the background chemotherapy (mFOLFOX6), unless preceded by disease recurrence, intolerable toxicity or withdrawal of consent.
As of March 2nd.,2020, dosing with IMP is stopped. Patients may continue their scheduled Treatment visits with mFOLFOX6 background therapy and without IMP until cycle 12, unless preceded by disease progression, intolerable toxicity or withdrawal of consent. If a patient discontinues oxaliplatin, an EOT visit will be done and the patients will continue in the Follow-up Phase.

If a patient discontinues oxaliplatin, treatment with 5-FU/folinate may be continued.

Following the completion of the Treatment Phase, patients may continue to receive mFOLFOX6 at the discretion of the Investigator,

Follow-up Phase

After the end of treatment (EOT) visit, patients will enter the Follow-up Phase and will have an Assessment Visit every 3 months from the first dose of IMP (±1 week) up to Month 12, then every 6 months (±1 week) up to Month 24. Any patient who discontinues from IMP for any reason (other than death or withdrawal of consent) will continue to have Assessment Visits (with the exception of tumor assessments for patients who have disease progression). As of March 2nd., 2020, from which date onwards no IMP is given anymore, any patient who discontinues from mFOLFOX6 for any reason (other than death or withdrawal of consent) will continue to have Assessment visits (with the exception of tumor assessments for patients who have disease recurrence).

End of Study (EOS)

Before March 2nd., 2020, for each patient, the Treatment Phase and Follow-up Phase lasted a total of 24 months (i.e. time from first dose of IMP to last Assessment Visit).
As of March 2nd., 2020, patients who are still in the Treatment Phase by the estimated data cut-off date of 30 September 2020, will have an EoT visit on day 14 ± 3 days of the last

mFOLFOX6 cycle.
As of March 2nd., 2020, for patients who are still in the Follow-up Phase by the estimated data cut-off date of 30 September 2020, the EOS will be within 1 week prior to the data cut-off date. EOS information (date, primary reason for EOS) can be collected during on-site assessment visit if applicable or over the phone or from any other available medical resource. At the EOS visit, all assessments planned for Month 24 visit (Follow-up Phase) will be performed.

Steering Committee

A Study Steering Committee (SSC) will be appointed by PledPharma AB prior to study start comprising 3-4 Investigators participating in the study and PledPharma AB representatives from the clinical study team.

The SSC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SSC will review protocol amendments as appropriate. The details of the role of the SSC will be defined in the Steering Committee Charter.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will monitor accumulating safety, efficacy and other types of data throughout the study. DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary. The complete roles and responsibilities of the DSMB and its membership will be defined in a separate Charter.

5.2.1 Study Procedures

All assessments will be performed according to the Schedule of Assessments in Appendix 1.

5.2.1.1 Screening Period

As of March 2nd., 2020, no more patients will be screened. This section further describes how screening was done before March 2nd., 2020.
Evaluations to determine the patient's study eligibility will be performed ≤28 days before the first dose of IMP (Treatment Visit 1) and will include the following:

- Written informed consent must be obtained prior to any study-specific evaluations being performed. Results of all pre-treatment evaluations must be reviewed by the Investigator (or his/her designee) to ensure that all eligibility criteria have been satisfied prior to patient enrollment
- HbA1c assessment for patients with history of diabetes. For patients with a history of diabetes mellitus, HbA1c assessment will be performed. Assessments performed as Standard of Care before the Informed Consent Form signature, but within 28 days prior to the first IMP dose are acceptable.
- Computer tomography (CT) or MRI scan (of thorax, abdomen and pelvis) and disease assessment (according to RECIST v1.1); results from a scan performed ≤42 days before surgery (or after surgery) are acceptable.
- Blood manganese (Mn) sample

Within 7 days prior to randomization:

- Carcinoembryonic antigen (CEA)
- Medical history (including an assessment of conditions and symptoms present at baseline) and prior medications (including those medications taken 30 days prior to first dose of IMP)
- Physical examination (including height and weight measurements, and a neurologic assessment performed prior oxaliplatin treatment according to local practice)
- Vital signs (including temperature, pulse rate, and blood pressure)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Serum β-human choriongonadotropin pregnancy (β-HCG) test in women of childbearing potential (WOCBP)
- Demography
- Hematology sample to assess white blood cell (WBC) count differential, absolute neutrophil count (ANC), red blood cell (RBC) count, platelet count and hemoglobin (to be analyzed by a local laboratory)
- Serum biochemistry sample to assess ALP, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine and albumin (to be analyzed by a local laboratory)
- 12-lead ECG
- The Cold Sensitivity questionnaire (paper diary)

5.2.1.2 Randomization

As of March 2nd., 2020, no more patients will be randomized.
This section further describes how randomization was done before March 2nd., 2020.
When the Investigator confirms that a patient complies with all inclusion/exclusion criteria, the patient will be randomized into 1 of 2 treatment arms (1:1) using the electronic randomization system within the electronic case report form (eCRF). This is not a patient visit.

The Investigator will then request the unblinded pharmacist/designee to prepare the IMP according to the randomization schedule available only to the unblinded hospital staff.

5.2.1.3 Treatment Phase

Each treatment cycle of chemotherapy will last for 2 weeks.

Treatment Visit 1 (Week 0): Day 1 of Cycle 1 of mFOLFOX6 chemotherapy

As of March 2nd., 2020, no patients will be having a Treatment Visit 1 anymore.
This section below describes how Treatment Visits 1 were done before March 2nd., 2020.

Before IMP infusion

- Concomitant medications
- Vital signs and weight
- ECOG performance status
- Check of hematology, biochemistry and serum β-HCG pregnancy test results from samples taken within 7 days prior to Randomization or from new samples prior to start of infusion at Treatment Visit 1
- Review of results of blood Mn sample

- FACT/GOG-NTX-13
- Grooved pegboard
- Vibration sensitivity test, performed using a graduated tuning fork
- EQ-5D-5L questionnaire
- Pain NRS questionnaire
- Health economic impact
- AEs

IMP infusion

- PledOx or placebo will be administered by an i.v. infusion over approximately 10 minutes, 15 minutes prior to mFOLFOX6

After IMP infusion

- AEs

mFOLFOX6 infusion

Treatment Visits 2, 3, 4, 5, 6 (Weeks 2, 4, 6, 8, 10 ±2 days)

Assessments at these visits are similar to Treatment Visit 1 with the following exceptions:

- Biochemistry parameters are assessed every 4 weeks i.e. Treatment Visit 3 and 5 only (samples to be taken in advance of the visit to have the results available before the start of the new chemotherapy)
- EQ-5D-5L, is assessed at Treatment Visit 4 only
  As of March 2nd., 2020, no more Blood Mn samples are taken with the exception for patients with Parkinson-like symptoms.
  During the COVID-19 pandemic, remote data collection via either telephone call or mailing of rating scales may be implemented for EQ-5D-5L
- The Cold Sensitivity questionnaire (paper diary) is completed before mFOLFOX6 infusion at Treatment Visits 2 and 4; and on Days 1, 2, and 3 after the mFOLFOX6 infusion at Day 1
  During the COVID-19 pandemic, remote data collection via either telephone call or mailing of the Cold Sensitivity Questionnaire may be implemented.
- Health economic impact data are not collected at these visits
- In case the chemotherapy are delayed and the patient is present at hospital, the patient should complete the predose assessments and the results will be recorded in EDC. When a patient comes for a delayed treatment visit, the predose assessments will be completed before the treatment and the results will be recorded in EDC as an unscheduled visit. If the delay is 14 days or more, it should be repeated again. For details please refer to the last version of eCRF completion guideline.

Assessment Visit: Month 3 (Week 12±1 week)

During the COVID-19 pandemic, a visit window of ±6 weeks is allowed for the Assessments Visits.

During the treatment phase, the assessment visits will be calculated on a weekly basis, i.e., Month 3 corresponds to Week 12 ±1 week.

Note: If the patient continues with mFOLFOX6, relevant Treatment Visit will be combined with the Month 3 Assessment Visit. The Assessment Visit at Month 3 will be performed as a separate visit only if a patient stops **mFOLFOX6** prior to Treatment Visit 7 (Week 12). In this case, Assessment Visit at Month 3 can be combined with End of Treatment (EOT) visit if EOT visit is performed 3 months after first IMP dose.

If a patient terminated the mFOLFOX6 prior to Month 3, the Month 3 visit will be calculated as 3 months (± 1 week) after C1D1.

The following assessments will be performed at each Assessment Visit:

- Concomitant medications (up to 30 days after the EOT visit)
- Physical examination
- Vital signs
- ECOG performance status
- Hematology sample
- FACT/GOG-NTX-13
- Grooved pegboard
- Vibration sensitivity test, performed using a graduated tuning fork
- EQ-5D-5L
- Pain NRS questionnaire
- AEs
- DFS
- During the COVID-19 pandemic, remote data collection via either phone call or mailing of rating scales may be implemented for ECOG performance status; FACT/GOG-NTX-13; EQ-5D-5L; Pain NRS questionnaire, AEs.

Treatment Visit 7, 8, 9, 10, 11, 12 (Weeks 12, 14, 16, 18, 20, 22 ±2 days)

Assessments at these visits are similar to Treatment Visit 1 with the following exceptions:

- Biochemistry parameters are assessed every 4 weeks i.e. Treatment Visit 7, 9 and 11 only (samples to be taken in advance of the visit to have the results available before the start of the new chemotherapy)
- QoL/health status (EQ-5D-5L) is assessed at Treatment Visits 8 and 12 only. During the COVID-19 pandemic, remote data collection via either phone call or mailing of EQ-5D-5L may be implemented.
- As of March 2nd., 2020, no more Blood Mn samples are taken with the exception for patients with Parkinson-like symptoms.
- The Cold Sensitivity questionnaire (paper diary) is completed before mFOLFOX6 infusion at Treatment Visit 8 and on Days 1, 2, and 3 after mFOLFOX6 infusion at day 1.
  During the COVID-19 pandemic, remote data collection via either telephone call or mailing of Cold Sensitivity Questionnaire may be implemented.
- Health economic impact data are not collected at these visits
- In case the chemotherapy are delayed and the patient is present at hospital, the patient should complete the predose assessments and the results will be recorded in EDC. When a patient comes for a delayed treatment visit, the predose assessments will be completed before the treatment and the results will be recorded in EDC as an unscheduled visit. If

the delay is 14 days or more, it should be repeated again. For details please refer to the last version of eCRF completion guideline.

Assessment Visit: Month 6 (Week 24±1 week)

During the treatment phase, the assessment visits will be calculated on a weekly basis, i.e., Month 6 corresponds to Week 24 ±1 week.
During the COVID-19 pandemic, a visit window of ±6 weeks is allowed for the Assessments Visits.

Note: If the patient continues with mFOLFOX6 without IMP until Treatment Visit 12 (Week 22), the relevant Treatment Visit or the EOT Visit will be combined with the Assessment Visit at Month 6. The Assessment Visit at Month 6 will be performed as a separate visit only if a patient stops mFOLFOX6 prior to Treatment Visit 12 (Week 22).

If a patient terminated mFOLFOX6 without IMP prior to Month 6, the Month 6 visit will be calculated as 6 months (± 1 week) after C1D1.

Assessments will be as per the Assessment at Month 3 (see above) with addition of health economic impact data collection.

EOT Visit

The following assessments will be performed at Day 14 (±3 days) of the last cycle of mFOLFOX6 (without IMP) before Cycle 12 or at Cycle 12 (whichever comes first) :

- CEA
- Concomitant medications (up to 30 days after the EOT visit)
- Physical examination
- Vital signs and weight
- ECOG performance status
- Hematology sample
- Biochemistry sample
- Blood Mn sample
  As of March 2nd., 2020, no more Mn samples are being taken except in case of Parkinson-like symptoms
- FACT/GOG-NTX-13
- Grooved pegboard
- Vibration sensitivity test, performed using a graduated tuning fork
- EQ-5D-5L
- Pain NRS questionnaire
- AEs
- During the COVID-19 pandemic, remote data collection via either phone call or mailing of rating scales may be implemented for ECOG performance status; FACT/GOG-NTX-13; EQ-5D-5L; Pain NRS questionnaire, AEs.

Concomitant medications will be recorded until 30 days after the EOT visit.All AEs including SAEs will be collected up to 30 days after the EOT visit and followed until

resolution.

5.2.1.4 Follow-up Phase

During the follow-up period, visit dates are calculated on a monthly calendar basis after C1D1. All patients will be followed for 24 months from first dose of IMP, with Assessment Visits every 3 months until Month 12 and every 6 months thereafter. Any patient who discontinued from mFOLFOX6 for any reason during the treatment phase other than death or withdrawal of consent will continue to have CIPN and tumor assessments every 3 months.
As of March 2nd., 2020, patients will have their assessment visits until the estimated data cut-off date by 30 September 2020.
An EOS visit will be done within 1 week of the data cut-off date.
At the EOS visit, all assessments planned for Month 24 visit (Follow-up Phase) will be performed.

Assessment Visits: Months 9, 12, 18, and 24 (±1 week)
During the COVID-19 pandemic, a visit window of ± 6 weeks is allowed.

- CT or MRI scan and disease assessment (at Month 12 and Month 24 [EOS] only)
- CEA (at Month 12 and Month 24 [EOS] only)
- Physical examination
- Vital signs
- ECOG performance status
- FACT/GOG-NTX-13
- Grooved pegboard
- Vibration sensitivity test, performed using a graduated tuning fork
- EQ-5D-5L
- Pain NRS questionnaire
- Health economic impact (at Months 12, 18 and 24 only)
- DFS
- During the COVID-19 pandemic, remote data collection via either phone call or mailing of paper copies of rating scales may be implemented for ECOG performance status; FACT/GOG-NTX-13; EQ-5D-5L; Pain NRS questionnaire, Health Economic Impact.

5.3 RANDOMIZATION AND BLINDING

5.3.1 Randomization

Randomization will be performed after eligibility has been confirmed and within 3 days prior to the start of infusion of the first cycle of mFOLFOX6 chemotherapy.

Patients will be randomized in blocks into 1 of 2 arms in a 1:1 ratio using the electronic randomization system within the eCRF:

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

5.3.2 Blinding

This is a double-blind, placebo-controlled study. Blinding is critical to the integrity of this clinical study.

The IMP will be prepared by a qualified unblinded pharmacist/designee not otherwise involved in the study to ensure the blinding. The unblinded pharmacist/designee will prepare the IMP in an amber colored syringe masking the colored appearance on the IMP or another type of syringe depending on site procedure. The prepared IMP, i.e. the syringe and amber colored tubing (or any other system maintaining the blinding depending on site preference), is provided to the blinded nurse who will perform the administration, not knowing which treatment is given, or to an unblinded nurse not performing any other assessment in the study. The blinding of the patient will be maintained in any case, but the process in each site may differ. Thus, the process at each site will be closely monitored from the initiation and regularly assessed during the study.

5.4 STUDY TREATMENTS

5.4.1 Identity of Investigational Medicinal Product

PledOx and placebo will be supplied to each site. All used and unused IMP must be kept at the site for accountability purposes.

Batch number(s) and expiry date(s) will be documented in the Drug Accountability Log in the Trial Master File and will be included in the final Clinical Study Report (CSR).

5.4.2 Packaging

PledOx in colorless glass vials, each containing 20 mL of solution, will be packed into a kit. Each kit will contain 4 vials. Kits will be transported frozen within -25°C to -15°C.

Placebo vials, each containing 20 mL of solution, will be packed into a kit. Each kit will contain 4 vials. Kits will be transported at ambient temperature, i.e. within 15°C to 25°C.

5.4.3 Labelling

A booklet label in the local language and in compliance with applicable regulations and guidelines will be attached to the vials and the kits.

Each vial label will have a detachable part containing vial and batch number. This part will be removed by the unblinded pharmacist/designee preparing the correct dose and stuck onto the unblinded drug accountability log.

5.4.4 Storage

All IMP (i.e. PledOx or placebo) should be stored in a safe place with limited access.

PledOx (vials) is to be protected from light and stored frozen at -15°C to -25°C.

The standard procedure is to thaw the IMP at 5°C ± 3°C (41°F± 5°F) overnight before the planned infusion preparation. If needed there is also a possibility to thaw the vial by holding it in the hand for at least 5 minutes for defrosting, shortly before the planned infusion (i.e. at the day of infusion). Thawed vials can be stored at 5°C ± 3°C for maximum 6 days. An unopened vial may be thawed and refrozen once. The thawed vial needs to be refrozen the same day.

The non-diluted IMP (50 mM solution) is stable in room temperature (i.e. 20°C to 25°C [68°F to 77°F]) for a maximum of 24 hours. The diluted solution (prepared syringe) is stable for 3 hours in room temperature (i.e. 20°C to 25°C [68°F to 77°F]) or 5 hours when refrigerated at 2°C to 8°C (36°F to 46°F). If refrigerated, the diluted IMP should come to room temperature before administration (storage in room temperature following the 2°C to 8°C storage can be allowed for 1 hour).

Temperature logs must be kept for the freezer and refrigerator where the IMP is stored. The log should be updated by site personnel twice per week (unless automatic temperature readings are available).

Placebo will be stored within ambient temperature.

5.4.5 Destruction of IMP

The unblinded monitors should account for all IMP at the study site. However, there is no need to account for used IMP vials by the unblinded monitor before the destruction of the IMP if the entire IMP use and destruction is documented in the patient and study accountability logs. All IMP will be accounted for and disposed at the sites. Unused IMP vials should be kept and sent for destruction (if applicable).

5.4.6 Background Therapy

All background therapy, i.e. non-IMPs, will be used according to their respective approved Summary of Product Characteristics (SmPC).

5.5 Duration of Study Participation

During the Treatment Phase, enrolled patients will receive IMP (i.e. PledOx or placebo) on top of mFOLFOX6 chemotherapy. Subsequently, patients will attend Follow-up visits every 3 months for the first 12 months and then every 6 months up to 24 months.

The entire study will run for approximately 24 months from first dose of IMP.

An estimated data cut-off date will be implemented by 30 September 2020 when all patients should discontinue study participation.

5.6 Discontinuation Criteria

The discontinuation criteria for individual patients, parts of study and the entire study are presented in Sections 6.3 to 6.5.

5.7 Investigational Product Accountability

It is the responsibility of the Investigator to establish a system for handling the IMP and to ensure that:

- Deliveries of such products are correctly received and recorded by a designated and properly trained person
- IMP are handled and stored safely and properly
- IMP is prepared by an unblinded pharmacist/designee who has no other contact with the patient, and is not involved in any other care or recording of any data related to the study
- IMP are given only to study patients in accordance with the protocol

- All unused IMP and empty vials are stored until they have been checked by the monitor
- It is possible to reconcile records of all used and unused stocks as confirmed by Investigator's signature

5.8 CODE BREAKS

Unblinding will be controlled through the randomization system. In case of such emergency that it is crucial for the Investigator (or any other treating physician) to know whether the patient has received PledOx or placebo, unblinding can be requested in the system. If unblinding occurs, this must be documented in the patient's hospital records with date and name of the Investigator who decided to unblind the study treatment. The Sponsor must be notified prior to unblinding, except in cases where an immediate need for unblinding exists for reasons of patient safety at which time the Investigator can unblind the patient prior to notifying the Sponsor. However, the Investigator will have the final decision and unilateral right for unblinding in matters involving the safety of study patients.

In the event of an SAE, the Investigator may unblind the study treatment if the appropriate future management of the patient necessitates knowledge of the current treatment. Although it is advantageous to retain the blind for all patients prior to final study analysis, when a SAE may be a serious adverse reaction unexpected or otherwise judged reportable on an expedited basis, it is recommended that the blind should be broken only for that specific patient, by the sponsor, even if the Investigator has not broken the blinding.

The treatment code will not be broken until all assessments have been performed, all data have been entered into the database and the database has been locked after a formal clean file has been produced.

The DSMB will monitor data according to the DSMB Charter.

5.9 SOURCE DATA

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verifies the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the study. They include laboratory notes, memoranda, material dispensing records, patient files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the monitor at each monitoring visit. The Investigator must submit a completed eCRF for each patient who signed the Informed Consent Form (ICF). All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study ID and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

5.10 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Oxaliplatin, in combination with 5-FU plus folinate (or capecitabine), has increased survival in stage III CRC and prolonged life in stage IV patients, but its use is compromised because of severe toxicity. CIPN is the most problematic dose-limiting toxicity of oxaliplatin. No treatments have been clinically proven to prevent CIPN. There is a body of evidence that CIPN

is caused by cellular oxidative stress. Clinical and preclinical data suggest that the Mn chelate and superoxide dismutase mimetic MnDPDP and (PledOx, $Ca_4Mn(DPDP)_5$) are efficacious inhibitors of CIPN and other conditions caused by cellular oxidative stress, without interfering negatively with the tumoricidal activity of chemotherapy. MnPLED, the main active metabolite of $Ca_4Mn(DPDP)_5$, can potentially modulate cellular oxidative stress at several critical levels such as superoxide generation, peroxynitrite formation and inactivation of the SOD-enzyme as well as hydroxyl radical formation. Results from a placebo-controlled, Phase 2 study (PLIANT) suggest efficacy of calmangafodipir in preventing CIPN.

Since no pharmacologic intervention can be recommended for the prevention of CIPN, placebo controlled studies are appropriate. It is acknowledged that 2 studies, 1 in the adjuvant setting and 1 in the metastatic setting (excluding adjuvant exposed patients) will present a favorable study program. A study in the adjuvant setting alleviates the concerns about the heterogeneity in patient population, and available chemotherapy combinations/regimens as well as potential confounding from treatment breaks. A study in the metastatic setting allows assessment of absence of signs of a detrimental effect on the underlying treatment.

PledPharma AB has designed the POLAR-A study for the continued development of PledOx with the ambition of forming the basis for registration.

Overall, it can therefore be concluded that there is a clear unmet medical need for the prevention of CIPN, and the PLIANT data justifies a confirmatory study of PledOx in this setting.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1 PATIENT INCLUSION CRITERIA

Patients are eligible to be included in the study if they meet the following criteria:

1. Signed informed consent form before any study related assessments and willing to follow all study procedures.
2. Male or female aged ≥18 years.
3. Pathologically confirmed adenocarcinoma of the colon or rectum including: Stage III carcinoma (any T N1,2 M0) or Stage II carcinoma (T3,4 N0 M0).
4. The patient has undergone curative (R0) surgical resection performed within 12 weeks prior to randomization.
5. The patient has a postsurgical CEA level ≤1.5x upper limit of normal (ULN, in current smokers, CEA level ≤2.0 x ULN is allowed).
6. No prior anti-cancer therapy for CRC except radiotherapy or concomitant chemo-radiotherapy using a fluoropyrimidine alone for locoregional rectal cancer.
7. Patient indicated for up to 6 months of oxaliplatin-based chemotherapy and without pathological findings of a neurologic exam performed prior to oxaliplatin treatment according to local practice.
8. ECOG performance status of 0 or 1.
9. Adequate hematological parameters: hemoglobin ≥100 g/L, ANC ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L.
10. Adequate renal function: creatinine clearance >50 cc/min using the Cockcroft and Gault formula or measured.
11. Adequate hepatic function: total bilirubin ≤1.5 x ULN (except in the case of known Gilbert's syndrome); AST and ALT ≤3 x ULN.
12. Baseline blood Mn level <2.0 x ULN.
13. For patients with a history of diabetes mellitus, HbA1c ≤7%.
14. Negative pregnancy test for WOCBP.
15. For men and WOCBP, use of adequate contraception (oral contraceptives, intrauterine device or surgically sterile) while on study drug and for at least 6 months after completion of study therapy.

6.2 PATIENT EXCLUSION CRITERIA

Patients will be ineligible if 1 or more of the following statements are applicable:

1. Any evidence of metastatic disease.
2. Any unresolved toxicity by NCI-CTCAE v.4.03 >Grade 1 from previous anti-cancer therapy (including radiotherapy), except alopecia.
3. Any grade of neuropathy from any cause.
4. Any evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, cardiac, unresolved bowel obstruction, hepatic or renal disease).
5. Chronic infection or uncontrolled serious illness causing immunodeficiency. Patients with known history of chronic hepatitis B can be enrolled if they are asymptomatic and an acute and active HBV infection can be excluded.
6. Any history of seizures.
7. A surgical incision that is not healed.

8. Known hypersensitivity to any of the components of mFOLFOX6 and, if applicable, therapies to be used in conjunction with the chemotherapy regimen or any of the excipients of these products.
9. History of other malignancies (except for adequately treated basal or squamous cell carcinoma or carcinoma in situ) within 5 years, unless the patient has been disease free for that other malignancy for at least 2 years.
10. Known dihydropyrimidine dehydrogenase deficiency.
11. Pre-existing neurodegenerative disease (e.g., Parkinson's, Alzheimer's, Huntington's) or neuromuscular disorder (e.g., multiple sclerosis, amyotrophic lateral sclerosis, polio, hereditary neuromuscular disease).
12. Major psychiatric disorder (major depression, psychosis), alcohol and/or drug abuse.
13. Patients with a history of second or third-degree atrioventricular block or a family heredity.
14. A history of a genetic or familial neuropathy.
15. Treatment with any investigational drug within 30 days prior to randomization.
16. Pregnancy, lactation or reluctance to using contraception.
17. Any other condition that, in the opinion of the Investigator, places the patient at undue risk.
18. Previous exposure to mangafodipir or calmangafodipir.
19. Welders, mine workers or other workers in occupations (current or past) where high Mn exposure is likely.

6.3 PATIENT WITHDRAWAL CRITERIA

6.3.1 Removal of Patients from Therapy or Assessment

The patient will be advised in the ICF that they have the right to withdraw from the study at any time without providing an explanation and without affecting their right to an appropriate follow-up investigation.

Once a patient has been included in the study, the Investigator should make every reasonable effort to keep the patient in the study.

Patients may be discontinued from the study at any time at the discretion of the Investigator, the Covance or the Sponsor. In the event that the patient drops out of the study or is withdrawn from the study, the withdrawal page in the patient's eCRF should be completed, including the date and reason for withdrawal. Specific reasons for discontinuing a patient from further assessments include:

- Withdrawal of informed consent
- Patient lost to follow-up (i.e. drop-outs)
- Death
- Substantial Clinical Study Protocol violation
- The Investigator's decision
- Pregnancy

Patients who discontinue from IMP for any reason (other than death or withdrawal of consent) will continue to have Assessment Visits (with the exception of tumor assessments for patients who have disease recurrence), as per protocol.

As of March 2nd., 2020, no new patients can be included in the study and all patients should be discontinued from IMP. Patients who are still in the treatment phase and continue on mFOLFOX6 will continue the planned Treatment Phase Visits till Cycle 12 and EOT; following which they will move into the follow-up phase and have Assessment Visits.
At the time of the data cut-off date estimated by 30 September 2020, all patients will discontinue the study.

Any AEs must be followed until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve because of the patient's underlying condition, even after withdrawal from the study.

Patients withdrawn from the study will not be replaced.

The Investigator will make every reasonable effort to complete the procedures outlined for the end of treatment visit for patients who has received study medication and are subsequently withdrawn from the study.

6.3.1.1 Stop Criteria

Stop criteria are as follows:

- Any patient who has elevated Mn levels (>2 times ULN) confirmed by MRI that shows Mn accumulation should be immediately withdrawn from further treatment with the IMP.
- Patients may be withdrawn from the IMP treatment at the discretion of the Investigator.
- Pregnant study patients must be withdrawn from treatment immediately, whereas male patients may continue in the study should pregnancy of female partners occur.
- Disease progression
- Patients with a seizure, regardless of intensity, or an anaphylactoid reaction/allergic infusion reaction (hypersensitivity), with moderate or severe intensity and judged to be related to IMP should discontinue dosing.
- Intolerable toxicity.
- As of March 2nd., 2020, all patients have to stop IMP but may continue on mFOLFOX6.

6.3.2 Pregnancy

Sexually active males and WOCBP, must use adequate contraception (see below; oral contraceptives, intrauterine device or surgically sterile) while on study drug and at least 6 months after the completion of the chemotherapy.

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly Effective Methods That Are User Independent[1]

• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation o Oral o Intravaginal o Transdermal
• Progestogen only hormonal contraception associated with inhibition of ovulation o Oral o Injectable o Implantable[2]
• Intrauterine device (IUD)[2] • Intrauterine hormone-releasing system (IUS)[2] • Bilateral tubal occlusion[2]
• **Vasectomized partner[2]** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

[1]: Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.
[2]: Contraception methods that in the context of this guidance are considered to have low user dependency

WOCBP must have a negative pregnancy test at Screening to be eligible for enrolment. Pregnancy testing should be done monthly and maintained until the end of systemic exposure to IMP.

6.4 PREMATURE TERMINATION OF STUDY IN A STUDY CENTER

The study may be terminated at an individual study site if it becomes apparent that patient enrolment is unsatisfactory with respect to quality and/or quantity. Sites may also be closed if they prove to be unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete.

In a case where the study is terminated in an individual site for any reason, the Investigator must make every effort to follow up all patients as planned according to the protocol. Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and regulatory authorities will be informed about reason and time of termination according to the applicable laws and regulations.

An initiative for site closure or study termination can be taken at any time either by the Sponsor or by the Investigator, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for such action taken by the Sponsor include, but are not limited to the following:

- Successful completion of the study at the site
- The required number of patients for the study has been recruited

- Failure of the Investigator to comply with the protocol, the Sponsor's procedures, or GCP/regulatory guidelines
- A major protocol violation was identified or developed during the study
- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of patients by the Investigator

Replacement of sites is allowed, and new sites may be initiated.

6.5 TERMINATION OF STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Investigator should notify the IEC/IRB in writing of the study's completion or early termination and send a copy of the notification to the Sponsor.

6.6 FURTHER TREATMENT AFTER THE END OF THE TREATMENT PHASE

Following the completion of the Treatment Phase, patients may continue to receive mFOLFOX6 at the discretion of the Investigator, but without IMP on top, as part of the Follow-up Phase.

As of March 2nd., 2020, the EOT Visit will be done at Day 14 (± 3 days) at Cycle 12 for patients who, at the discretion of the Investigator, continue mFOLFOX6 treatment beyond Cycle 12.
Patients who are still in the Treatment Phase by the estimated data cut-off date of 30 September 2020, will have an EoT visit on day 14 ±3 days of the last mFOLFOX6 cycle.

Concomitant medications and SAEs/AEs will be recorded until 30 days after the EOT visit.

7. TREATMENT OF PATIENTS

7.1 TREATMENTS ADMINISTERED

7.1.1 Investigational Product

PledOx drug product is composed of the drug substance in an aseptically prepared, sterile filtered, aqueous formulation for parenteral administration using compendial excipients. Clinical formulations consist of 50 mM calmangafodipir provided as a sterile, bright yellow clear solution in 20 mL colorless, single dose, glass vials. The pH is adjusted between 7.4 and 7.6 with sodium hydroxide.

The active ingredient is calmangafodipir. Other excipients are sodium chloride, sodium hydroxide and water for injection.

PledOx, corresponding to 5 µmol/kg calmangafodipir, will be given to patients as an i.v. infusion, on top of mFOLFOX6 chemotherapy.

7.1.2 Control Product

Placebo: 0.9% sodium chloride in 20 mL vials.

Placebo will be administered via the same route as PledOx (i.v. infusion).

7.1.3 Background Therapy

All patients will be treated with mFOLFOX6 chemotherapy given in 2-week cycles. mFOLFOX6 is administered on Day 1 and 2 of each cycle as specified in **Table 2**.

Background therapy will be used according to their respective approved SmPC.

7.2 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

The patients will be randomized in a 1:1 ratio:

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

Randomization is performed centrally using an Interactive Web Response System.

7.3 SELECTION OF DOSES IN THE STUDY

The suggested dose of 5 µmol/kg has sufficient support in the PLIANT data (refer to the Investigator's Brochure [IB]). The 5 µmol/kg dose is the preferred dose based on available data, with an OR = 0.12 (p=0.018) vs placebo on the variable most like the primary endpoint in the POLAR studies (i.e. percentage of patients with patient-reported Leonard scoring 3 or more on either numbness, tingling or burning pain/discomfort with cold at FU2, which is approximately 10 months after first dose). Current knowledge suggests the dose in question has an acceptable safety and tolerability profile.

7.4 SELECTION AND TIMING OF DOSE FOR EACH PATIENT

7.4.1 PledOx/Placebo Administration

PledOx/Placebo will be administered by an i.v. infusion over approximately 10 minutes, 15 minutes prior to each mFOLFOX6 cycle. As a premedication antihistamine, diphenhydramine (1–2 mg/kg or 25–50 mg) shall be given slowly via i.v. in combination with ranitidine (50 mg diluted in 5% dextrose to a total volume of 20 mL) over approximately 5 min (Roselló et al. 2017). Alternative products, doses, or ways of administrations of anti-histamines to those given above may be used, according to local clinical practice.

Table 1 PledOx/Placebo Administration Schedule

Arm	Drug Dose*	Administration	Duration	Infusate/ Preparation	Time point
A+B *	Diphenhydramine (1–2 mg/kg or 25–50 mg). ranitidine (50 mg)	Shall be given slowly via i.v. in combination	Approximately 5 min	Ranitidine diluted in 5% dextrose to a total volume of 20 mL	Approximately 5 min before IMP
A**	PledOx 5 µmol/kg	i.v. infusion	Approximately 10 minutes	Ready-to-use formulation	Approximately 15 minutes prior to start of chemotherapy (Day 1 of each cycle)
B**	Placebo				

* Alternative products, doses, or ways of administrations of anti-histamines to those given above may be used, according to local clinical practice.

** A specific template for dose calculation will be provided all patients will receive 20 mL i.e. the volume of PledOx/placebo will be based on body weight

PledOx comes as ready-to-use formulation in 20 mL glass vials containing PledOx calmangafodipir 50 mM.

Placebo comes as ready-to-use formulation in 20 mL glass vials containing 0.9% NaCl.

An unblinded person (pharmacist/designee) not otherwise involved in the study will prepare the IMP. Administration of the IMP will be done by a blinded treating nurse. If administration is done by an unblinded nurse, this should be well documented and this unblinded nurse should not be involved in any other assessment in the study. Vials containing either PledOx or placebo and the corresponding infusion set will be hidden from the patient and the blinded study team.

Further details about the drug preparation will be provided in the Instructions for Handling of IMP.

7.4.2 Chemotherapy (mFOLFOX6) Administration

All patients will receive 5-FU, calcium-folinate or calcium-levofolinate and oxaliplatin, according to the mFOLFOX6 regimen, and pre-treatment with anti-emetics and corticosteroids will be given, as specified in **Table 2** and the approved SmPC, approved label and national guidance. The infusion line and the port should be flushed between the administrations. This is particularly important between IMP and oxaliplatin administration.

Table 2 Chemotherapy Administration Schedule

Drug	Dose	Administration	Duration	Infusate/ Preparation	Time point
Ondansetron*	8 mg*	i.v. injection			At least 30 min prior to start of chemotherapy
Beta-methasone*	8 mg*	i.v. injection			At least 30 min prior to start of chemotherapy
Oxaliplatin	85 mg/m^2	i.v. infusion	0-2 hours	0.5 L glucose 5%	Start of chemotherapy (regarded as time point 0)
Ca-levofolinate or Ca-folinate	100 or 200 mg/m^2 200 or 400 mg/m^2	i.v. infusion i.v. infusion	0-2 hours 0-2 hours	0.5 L glucose 5% 0.5 L glucose 5%	Start of chemotherapy (regarded as time point 0)
5-FU	400 mg/m^2	i.v. bolus		Recommendation 50-100 ml NaCl 0.9%	Approximately 2 h after time point 0
5-FU	2400 mg/m^2	i.v. continued infusion	2-48 hours		Approximately 2 h after time point 0

* For anti-emetics and corticosteroids, alternative doses to those given above, or alternative products may be used, according to local clinical practice.

7.5 Dose Adjustment Criteria

Any dose change to the IMP (i.e. PledOx or placebo), chemotherapy (mFOLFOX6), or other therapy must be recorded in the eCRF, including the reason for the change.

7.5.1 Treatment Requirements and Delays

Prior to each administration of chemotherapy, the patient's hematology must be adequate (as per local practice), and all toxicities (other than alopecia) should be resolved to Grade 0 or 1.

In case of febrile neutropenia and the patient's recovery to Grade 0 or 1, please see Table 3 for dose reduction recommendations. All pre-treatment lab data including hematology, biochemistry, pregnancy testing, may not be older than 72 hours before Day 1 of applicable cycle.

If these criteria are not met at the time of a planned treatment, the following general rules for the management of treatment delays apply:

- In the case of mFOLFOX6 related toxicity (see Section 7.5.2), the start of the next cycle will be delayed until toxicities (other than alopecia) are resolved to Grade 0 or 1.
- If administration of mFOLFOX6 is delayed for more than 6 weeks (3 cycles) after the first day of the previous cycle due to toxicity, treatment with that therapy can be discontinued at the Investigator's discretion.

7.5.2 Chemotherapy Related Adverse Events and Dose Modification

The following sections include guidelines for dose modifications and delays associated with specific symptoms.

Every Grade 3 or 4 toxicity according to NCI-CTCAE v4.03 that, in the opinion of the Investigator, put the patient at risk should be evaluated and adequate dose reduction/treatment delay should be considered. All dose modifications and the reasons should be recorded in applicable sections of the eCRF.

If other symptoms not discussed in this protocol occur, the treating Investigator should be consulted regarding the appropriate course of action with regard to dose modification or delay.

7.5.2.1 Dose Modification of Oxaliplatin due to Neuropathy

Neuropathy dose modifications should be performed according to the table below (Table 3) but may also be performed according to local practice. Table 3 provides a guideline on the grade and duration of the toxicity and oxaliplatin dose modifications.

Table 3 Neuropathy Dose Modification of Oxaliplatin

Grade	Duration of Toxicity	
	1 - 7 days	**>7 days – persistent between treatment cycles**
1	No dose reduction	No dose reduction
2	No dose reduction	25% dose reduction*
3	Discontinue oxaliplatin	Discontinue oxaliplatin
4	Discontinue oxaliplatin	Discontinue oxaliplatin

*If repeat events of neurosensory toxicity occur; local practice should be followed with the management of the toxicities being fully documented in the patient's medical records

Modification of infusion duration of oxaliplatin: infusion time may be increased from 1-2 hours to 6 hours in case of NCI-CTCAE Grade ≤2 allergy or in case of laryngeal spasm syndrome.

If treatment with oxaliplatin must be stopped due to toxicity, treatment with 5-FU/folinate and IMP may be continued.

Table 4 Definition of Neuropathy According to NCI-CTCAE v4.03

Grade	Definition: Peripheral sensory neuropathy
Grade 0	No change or none
Grade 1	Asymptomatic; loss of deep tendon reflexes or paresthesia
Grade 2	Moderate symptoms, limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

ADL = activities of daily living

7.5.2.2 Central Nervous System Toxicity

All central neurologic toxicity should be evaluated by the Investigator and in case of Grade 3 and 4 toxicities, according to NCI-CTCAE v4.03, mFOLFOX6 treatment should be stopped until neurological symptoms is reduced to Grade 1 or 0.

7.5.2.3 Hematological Dose Modification of Oxaliplatin and 5-Fluorouracil

Prior to each administration of chemotherapy, the patient's hematology must be adequate (as per local practice), and toxicities should be resolved to Grade 0 or 1.

Hematological dose modifications (based on nadir) are recommended to be performed according to the table below (Table 5), but may also be performed according to the discretion of the investigator, according to local practice and in the interest of the patient.

Table 5 Hematological Dose Modification of Oxaliplatin and 5-FU

Neutropenia	**Duration (counting from pre-dose of the cycle)**	**Action**
Grade 3/4 first time	≤7 days	No dose reduction when recovered
Grade 3/4 second time	≤7 days	Dose reduction to 75% of full dose when recovered (which can mean dose delay)
Grade 3/4 first time	>7 days	Dose reduction to 75% of full dose when recovered (which can mean dose delay)
Grade 3/4 second time	>7 days	Dose reduction to 75% of previous dose when recovered (which can mean dose delay)
Febrile neutropenia	-	Dose reduction to 75% of previous dose when recovered (which can mean dose delay)
Platelet count decreased	**Oxaliplatin**	**5-FU**
Grade 1/2	No dose reduction	No dose reduction
Grade 3/4	Dose reduction 75%	Dose reduction 75%

Definition for neutropenia according to NCI-CTCAE v4.03 based on ANC:

- Grade 1: <Lower limit of normal - 1.5 x 10^9/L (<1500/mm^3)
- Grade 2: <1.5 x 10^9/L (<1500/mm^3) and ≥1.0 x 10^9/L (≥1000/mm^3)
- Grade 3: <1.0 x 10^9/L (<1000/mm^3) and ≥0.5 x 10^9/L (≥500/mm^3)
- Grade 4: <0.5 x 10^9/L (<500/mm^3)

Definition of platelet count decreased according to NCI-CTCAE v4.03

- Grade 1: <Lower limit of normal -75.0 x 10^9/L (<75.000/mm^3)
- Grade 2: <75.0 x 10^9/L (<75,000/mm^3) and ≥50.0 x 109/L (≥50,000/mm^3)
- Grade 3: <50.0 x 10^9/L (<50,000/mm^3) and ≥25.0 x 109/L (≥25,000/mm^3)
- Grade 4: <25.0 x 10^9/L (<25,000/mm^3)

7.5.2.4 Diarrhea Dose Modification of 5-Fluorouracil

Table 6 shows the dose modifications of 5-FU due to diarrhea.

Table 6 Diarrhea Dose Modification of 5-FU

Grade of toxicity	Diarrhea	5-FU dose
0	No diarrhea and no increase in stool frequencies	No dose reduction
1	<4 stools/day	No dose reduction
2	4-6 stools/day	Stop until resumed to Grade 1 or less 1st time: 100% 2nd time: 75% 3rd time: 50%
3	7-9 stools/day	Stop until resumed to Grade 1 or less 1st time: 75% 2nd time: 50%
4	≥10 stools/day	Stop treatment

7.6 CONCOMITANT MEDICATION

Medication history (prior medications) is needed prior to study start. Prescription medications, over-the-counter medications, and herbal products should be asked for. Any prior anti-cancer treatment should also be recorded.

The Investigator or designee should assess changes in concomitant medications throughout the study by asking the patient at each visit. Any changes reported by the patient should be recorded in the eCRF. Medications will be coded according to the World Health Organization's Anatomic Therapeutic Chemical classification system classification.

Any other anti-cancer treatment given during the study should be recorded as concomitant medications on the patient's eCRF.

Non-steroidal anti-inflammatory drugs and opioid analogues may be given as symptomatic treatment for neuropathic pain, other drugs prescribed for neuropathic pain may be used to treat side effects at the Investigator's discretion, however it is of major importance that all medications used is recorded in the concomitant medication log including start and end date and the dose.

The use of growth factors (i.e. granulocyte-colony stimulating factor [G-CSF]) in patients who require G-CSF or GM-CSF therapeutically will be allowed at the discretion of the Investigator and may also be used to treat side effects at the Investigator's discretion.

Prophylactic treatment for neuropathic pain (anti-depressants, anti-epileptics, local anesthetics) is not permitted, but may be used to treat side effects at the discretion of the Investigator.

Other rescue medication may be used as the discretion of the Investigator.

7.7 ASSESSMENT OF COMPLIANCE

Assessment of patient compliance is not applicable as the IMP is administered at the clinic by a blinded study nurse as an infusion. Trained medical personnel will administer the IMP (i.e. PledOx or placebo), mFOLFOX6 therapy (oxaliplatin, 5-FU, and FA).

The Investigator has the responsibility to ensure that all IMP dispensed is recorded in the accountability log and in the medical records.

8. ASSESSMENT OF EFFICACY

8.1 EFFICACY PARAMETERS

8.1.1 Primary Efficacy Variable

8.1.1.1 Neuropathy Assessment - FACT/GOG-NTX

The primary efficacy parameter will be chronic CIPN assessed using a patient reported outcomes questionnaire. The FACT/GOG-NTX-13 (Version 4) includes 13 items that measure the severity and impact of symptoms of neurotoxicity over the past 7 days. Patients rate each item from 0 ("not at all") to 4 ("very much"). These 13 items are summed to create a total score, ranging from 0 to 52. A major strength of this instrument is that it was developed with patient input. The FACT/GOG-NTX-13 is included in Appendix 2.

The key symptoms of numbness or tingling in the hands or feet, as well as discomfort, can also be assessed reliably using a subscale of the first 4 questions/items of the FACT/GOG-NTX-13 (i.e. FACT/GOG-NTX-4). The FACT/GOG-NTX-4 was described and further validated by Huang (2007) in gynecologic oncology patients receiving cisplatin/paclitaxel. The 4 items capture 80% if the treatment difference and more than 60% of the longitudinal change. The FACT/GOG-NTX-4 was also used on approximately 1720 patients in the multinational large (N=6088 patients, SCOT trial; Iveson et al. 2017) adjuvant study with either mFOLFOX6 or CapeOx in patients with stage III or high-risk stage II CRC. The 4 selected questions are the most responsive to change in the onset of peripheral neuropathy. Furthermore, CIPN-related numbness, tingling and discomfort in hands and feet was assessed by FACT/GOG-NTX-13 to evaluate the effect of duloxetine compared to placebo (Smith 2013). This is the study on which ASCO based its recommendation for the use of duloxetine in CIPN (Hershman 2014).

Patients will complete this questionnaire electronically (on a hand-held device/tablet) in the hospital, within 72 hours before mFOLFOX6 infusion (Day 1 of each mFOLFOX6 cycle) during the Treatment Phase and at each Assessment Visit. In case of technical issues with the device/tablet, the patient may provide the PRO on a paper and this will be recorded in the system remotely.
During the COVID-19 pandemic, the FACT/GOG-NTX-13 questionnaire may be completed during a telephone call or by completing the paper version of the scale that has been mailed to the patient's home, if a site visit is not feasible.

8.1.2 Secondary Efficacy Variables

8.1.2.1 Cold Sensitivity Questionnaire

Acute CIPN during chemotherapy will be assessed using the "Cold Sensitivity" patient questionnaire (see Appendix 3). The questionnaire (paper diary) will be completed according to the Schedule of Assessments (Appendix 1).

Each patient will be asked if they experienced sensitivity to touching cold items within the last 24 hours. Cold sensitivity will be rated 0 (not at all) to 10 (as bad as you can imagine).

During the COVID-19 pandemic the Cold Sensitivity questionnaire may be completed during a telephone call or by completing the paper version of the scale that has been mailed to the patient's home, if a site visit is not feasible.

8.1.2.2 Assessment of Dose Modifications of Oxaliplatin and 5-FU

It is the responsibility of the Investigator to evaluate the need for dose reduction and/or treatment delay of mFOLFOX6 based toxicities and AEs assessed according to NCI-CTCAE v4.03 being probably or definitely related to the mFOLFOX6 according to Section 7.5 of the protocol.

The dose of oxaliplatin and 5-FU administered per patient during mFOLFOX6 chemotherapy will be recorded. For both oxaliplatin and 5-FU, dose, number of cycles per patient, any dose reduction or delay and reason(s) for dose reduction/delay will be recorded in the eCRF.

8.1.2.3 Vibration Sensitivity Test

Vibration sensitivity will be assessed within 72 hours before mFOLFOX6 infusion, according to the Schedule of Assessments (Appendix 1), using the graduated tuning fork. The assessor needs to compare the first measured (recorded) value to the second measurement (recorded as well). If there is no significant difference, the first value can be used. If there is a significant difference (ie, >1), then a new measurement needs to be performed.

This test allows a reliable assessment of vibration perception using a 128-Hz graduated tuning fork. When the tuning fork is struck against the ball of the thumb, the base of the tuning fork is placed over the appropriate bony surface (i.e., lateral malleolus left and right) and the patient is asked to indicate the moment when the vibration is no longer detected. The intensity at which the patient no longer detects the vibration is reported on a scale of 0 to 8 (Martina et al. 1998; Cavaletti et al. 2004).

Detailed instructions will be provided by PledPharma AB in a separate procedure manual.

8.1.2.4 Grooved Pegboard Test

Functional impairment in the non-dominant hand will be assessed within 72 hours before mFOLFOX6 infusion, according to the Schedule of Assessments (Appendix 1), using the grooved pegboard.This is a manipulative dexterity test of visual-motor coordination and has been used in various settings in which neuropathy is a complication, including CIPN (Miaskowski et al. 2017).

Detailed instructions for will be provided by PledPharma AB in a separate procedure manual.

8.1.2.5 Pain Numerical Rating Scale

Pain (in hands or feet) will be assessed using a simple NRS (3 questions) shown in Appendix 4. Patients will complete the questionnaire within 72 hours before mFOLFOX6 infusion, according to the Schedule of Assessments (Appendix 1), on a tablet in the hospital. In case of technical issues with the device/tablet, the patient may provide the PRO on a paper and this will be recorded in the system remotely.

During the COVID-19 pandemic, the Pain Numerical Rating Scale may be completed during a telephone call or by completing a paper version of the scale that has been mailed to the patient's home, if a site visit is not feasible.

The 3 NRS questions will assess the worst pain in the hands and feet in the past week (7 days), pain on average, and pain right now. Questions are rated by the patient from 0 (no pain) to 10 (pain as bad as you can imagine).

8.1.2.6 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. It is often referred to as a QoL questionnaire. The EQ-5D-5L comprises 5 dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. There are 5 options (levels) under each domain. An example is shown in Appendix 5.

Patients should complete the EQ-5D-5L questionnaire within 72 hours before mFOLFOX6 infusion, according to the Schedule of Assessments (Appendix 1), on a tablet in the hospital. In case of technical issues with the device/tablet, the patient may provide the PRO on a paper and this will be recorded in the system remotely.

During the COVID-19 pandemic, the EQ-5D-5L may be completed during a telephone call or by completing a paper version of the scale that has been mailed to the patient's home, if a site visit is not feasible.

8.1.2.7 Health Economic Impact

The health economic impact will be assessed at Day 1 (before IMP infusion) and then at 6, 12, 18 and 24 months after the first dose of IMP 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).

Pharmacoeconomic analyses will be performed to assess the clinical and economic impact of PledOx vs placebo in a cost-effectiveness and budget impact analysis. The objective will be to summarize and evaluate treatment group differences in total resource use, patient burden and societal costs of disease and AEs.

During the COVID-19 pandemic, the Health Economic Impact may be assessed during a telephone call or by completing a paper version that has been mailed to the patient's home, if a site visit is not feasible.

9. ASSESSMENT OF SAFETY

9.1 SAFETY PARAMETERS

9.1.1 Adverse Events

9.1.1.1 Adverse Event Definition

An AE in this study is defined as any untoward medical occurrence in a patient after signing the ICF. The occurrence does not necessarily need to have a causal relationship with the IMP. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the administration of IMP, whether or not causally related.

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor who is scrutinizing relevant source data.

All AEs, including chemotherapy related toxicities, will be graded using the NCI-CTCAE v4.03.

Clarifications

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as "acute appendicitis" and the resulting appendectomy noticed under Comments. Pre-study conditions, which led to elective surgery during the time of the study, are not to be reported as AEs.

If an abnormal laboratory value or vital sign is associated with corresponding clinical signs and symptoms, the sign/symptom should be reported as the AE and the associated laboratory result or vital sign should be considered additional information that is to be collected in the eCRF.

9.1.1.2 Serious Adverse Events

An SAE in this study is defined as any untoward medical occurrence that meets 1 of the following criteria:

- Results in death*
- Is life threatening**
- Requires inpatient hospitalization*** or prolongation of existing hospitalization***
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other medically important condition

* If a death is an outcome of an event, the AE/SAE that result in the death should be recorded and reported as the SAE. Efforts to complete an autopsy should be made and documented in the clinical notes. All results should be reported.

** The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

*** Hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition during the study that has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above

Events deemed as serious must be reported to Covance and PledPharma AB within 24 hours after the Investigator's awareness of the SAE. This short time frame is in compliance with international regulations. All SAEs should be reported by the site staff in the eCRF.

If the eCRF is not accessible, in case of electronic system failure, etc. which may cause a delay in safety data reporting within the required timelines, the Investigator will use a paper SAE form for reporting to Covance by fax.

Covance Pharmacovigilance

Email: GlobalSAEinbox@covance.com

or

Fax: Europe: 00 800 529 34043

Taiwan: (886) 800 529 34043

South Korea: (82) 002 800 529 34043

Hong Kong: (852) 001 800 529 34043

Japan: IDC: (81) 0061010 800-529-34043

KDDI: (81) 001010 800-529-34043

NTT: (81) 0033010 800-529-34043

In such cases, the Investigator will also need to record the previously reported information on the SAE in the eCRF as soon as the system is available again.

The Covance contact details will be pre-printed on the SAE form distributed to all Investigators participating in the clinical trial.

If the initial report is not complete, it should be followed by submission of a more detailed report within 5 calendar days.

All SAEs must be followed until the Investigator assesses the event has returned to baseline or has resolved.

After receiving the SAE report form from the Investigator, PledPharma AB or designee will make a causality (relationship) assessment. The term SADR (Serious Adverse Drug Reaction) is to be used whenever either the Investigator or PledPharma AB or designee deems the SAE as possibly or probably related to the IMP.

If the event is not described before in any clinical study of PledOx, e.g. in the current IB, the event is a SUSAR (Suspected Unexpected Serious Adverse Reaction). PledPharma AB or

designee has the obligation to submit SUSAR reports electronically to the EudraVigilance database within:

- 7 calendar days if fatal or life-threatening (follow-up information within an additional 8 calendar days)
- 15 calendar days if non-fatal and non-life-threatening (follow-up information as soon as possible)

The following bodies are recipients of the reports, and procedures for such reports are familiar to PledPharma AB or designee:

- Competent authority
- European Medicines Agency
- The study approving IEC/IRB

PledPharma AB has delegated the task of reporting SADR/SUSARs to Covance, but has the ultimate responsibility for the fulfilment of these tasks. This delegation is enforced in a written note.

9.1.1.3 Pregnancy

Any pregnancy that occurs during study participation must be reported. Pregnant study patients must be withdrawn from treatment immediately, whereas male patients may continue in the study should pregnancy of female partners occur. In this case, a separate informed consent will be obtained from the female partner for collection of information regarding the pregnancy.

Each pregnancy must be reported to the Sponsor (or designee) within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the trial and considered by the Investigator as possibly related to the IMP, must be promptly reported to the Sponsor (or designee).

9.1.1.4 Treatment-Emergent Adverse Events

All AEs will be recorded in the eCRF.

Non-treatment emergent AEs will include any AEs that occur between informed consent and the first dose 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.

The Investigator is to record all directly observed AEs and all AEs spontaneously reported by the patient in the patient's records (source data) and in the eCRFs using concise medical diagnostic terminology. The diagnosis/cause of an AE should be recorded rather than the symptoms of the AE. If no diagnosis is available each sign and symptom should be recorded as individual AEs.

All AEs must be graded for:

- Seriousness
- Intensity
- Causality (possible relationship) to the IMP

The question asked will be "Have you had any health problems since your last evaluation?" If no AE has occurred during the period concerned, this should actively be noted in the eCRF.

All AEs including SAEs will be collected up to 30 days after the EOT visit and followed until resolution.

During the COVID-19 pandemic the AEs and SAEs may be collected by telephone call or by paper mailed to the patient's home for completion, if a site visit is not feasible.

9.1.1.5 Adverse Events of Special Interest

Only AESIs which are considered serious are reportable to the safety team.

Chemotherapy

Treatment-related toxicity of mFOLFOX6 chemotherapy will be assessed prior to each treatment cycle and reported as AEs. Chemotherapy related AEs of special interest may include, but are not limited to, peripheral sensory neuropathy, hematological toxicities, ANC, febrile neutropenia, WBC count, and thrombocytopenia. Chemotherapy related toxicity may enforce dose modifications and dose delays (see Section 7.5.2).

PledOx

PledOx related AEs of special interest may include, but are not limited to, seizures, anaphylactoid reactions, allergic infusion reactions (hypersensitivity) or diarrhea.

For patients whose Mn concentrations are >2 x ULN at Cycle 4, Cycle 8, Cycle 12, EOT, and any subsequent cycle when Mn sampling is scheduled (in case patients continue with mFOLFOX6 and IMP after Cycle 12), a brain MRI and neurological examination will be performed to evaluate any cerebral neurological impact (see Section 9.1.2.3). In patients who develop any Parkinson-like symptoms, an additional blood Mn sample will be collected and analyzed (see Section 9.1.3.6). If Mn levels are elevated (>2 x ULN), an MRI and neurological examination will be performed and evaluated. Refer to Figure 2 and Section 9.1.2.3.

As of March 2nd., 2020, no more blood Mn samples will be collected

9.1.1.6 Intensity of Adverse Events

The expression intensity of AEs means the intensity of the event in the opinion of the patient. The intensity of each AE is to be graded by the Investigator according to NCI-CTCAE v4.03. The severity is graded 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening) or 5 (death related to AE).

9.1.1.7 Causality to the Investigational Medicinal Product

The relationship between the IMP and each AE has to be classified by the Investigator using 1 of the following terms:

Not related: An AE for which there is no reasonable temporal association between its onset and administration of the IMP, or that can reasonably be

explained by other factors, including underlying disease, complications, concomitant drugs or concurrent treatment.

Note: Even if the Investigator feels there was no relationship to IMP, the AE experience is to be reported.

Unlikely to be related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possibly related: An AE for which there is a reasonable temporal association between its onset and administration of the IMP (including the course of treatment after withdrawal of the drug) for which other causal factors may not be excluded.

Probably related: An AE for which there is a reasonable temporal association between its onset and administration of the IMP, including the course after treatment withdrawal, and which is more likely to be explained by the test drug than by any other cause (e.g. underlying disease, complications, concomitant drugs or concurrent treatment).

Definitely related: An AE that is judged as undeniably related to administration of IMP. Factors taken into consideration when a definite relationship is assigned include whether the AE:

- Followed a clear temporal sequence from administration of IMP.
- Could not be possibly explained by the known characteristics of the patient's clinical state, environmental or toxic factors, other modes of therapy administered to the patient.
- Disappeared or decreased on cessation or reduction in dose of IMP.
- Reappeared or worsened when IMP was re-administered.
- Followed a response pattern known to be associated with administration of IMP.

9.1.1.8 Action Taken for Adverse Events

For each AE, the following options for 'Action taken' will be available on the eCRF:

- Dose not changed
- Dose reduced
- Dose delayed
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

9.1.1.9 Recording and Reporting Adverse Event/Intercurrent Illnesses

It is the responsibility of the Investigator to document all AEs that occur during the study. Patient entry into the study is defined as the time at which informed consent is obtained (this

must be before any Protocol-specific diagnostic procedures or interventions). All subsequent AEs must be reported regardless of whether or not they are considered drug related.

An AE includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes whether associated with the study drug and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Death is an outcome of an event. The AE that resulted in the death should be recorded and reported as the SAE. If an autopsy is performed, efforts should be made to obtain the results.

Progression of disease should not be reported as an SAE.

The Investigator must report in detail all adverse signs and symptoms which are either volunteered by patients or observed during or following the course of IMP administration on the appropriate eCRF page.

Included in the description should be the nature of the sign or symptom; the date of onset; date of resolution (duration); the severity; the relationship to study treatment or other therapy; the action taken (if any), and the outcome.

An unexpected (serious) AE is one not previously reported (in nature, severity or incidence) in the current IB, in the clinical plan, or elsewhere.

In the event of a serious or unexpected AE or ADR, the Investigator will immediately notify Covance Pharmacovigilance.

The IRB/IEC must be informed if the serious or unexpected AE, in the opinion of the Sponsor or the Investigator, is likely to affect the safety of the patients or the conduct of the study.

All Investigators participating in the study will also be notified of the unexpected SAEs.

9.1.1.10 Adverse Event Follow-up Procedures

All AEs including SAEs will be collected up to 30 days after the the EOT visit and followed until resolution.

During the COVID-19 pandemic, AEs and SAEs may be collected by phone or by paper mailed to the patient's home, if a site visit is not feasible.

9.1.2 Laboratory Evaluation

Blood samples for laboratory evaluation will be collected according to the Schedule of Assessments (Appendix 1).

In addition to the sample timepoints shown in the Schedule of Assessments, blood samples may be taken whenever necessary according to the Investigator's judgement (according to local guidelines and practice).

For each value outside the normal ranges, the Investigator should mark the value as "Clinically Significant" (CS) or "Not Clinically Significant" (NCS).

9.1.2.1 Hematology

Blood samples (approximately 4.5 mL per sample) for hematology evaluations should be collected by venipuncture or capillary sampling from the finger. The exact timepoint for collection of the samples will be noted in the eCRF.

Hematology: WBC count differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils), ANC, RBC count, platelet count, and hemoglobin.

Local laboratories will be used to analyze hematology samples.

9.1.2.2 Biochemistry

Blood (serum) samples (approximately 4.5 mL per sample) for biochemistry evaluations should be collected by venipuncture. The exact timepoint for collection of the samples will be noted in the eCRF.

Biochemistry: Alkaline phosphatase (ALP), total bilirubin, ALT, AST, serum creatinine, and albumin.

Local laboratories will be used to analyze biochemistry samples.

9.1.2.3 Blood Manganese

As of March 2nd., 2020, Blood Manganese testing will only be done in patients with Parkinson-like symptoms following previous use of IMP.

Before March 2nd., 2020, Blood samples (approximately 6.0 mL per sample) will be collected for assessment of Mn at Screening and at timepoints according to the Schedule of Assessments (Appendix 1) at the day of treatment and before IMP infusion.

Figure 2 shows a flow chart of monitoring increased Mn levels and/or Parkinson-like symptoms. Patients that show Mn concentrations >2 x ULN at Cycle 4, Cycle 8, Cycle 12, EOT, and any subsequent cycle when Mn sampling is scheduled (in case patients continue with mFOLFOX6 and IMP after Cycle 12) will be referred to a brain MRI investigation and a neurological examination (see Section 9.1.3.6).

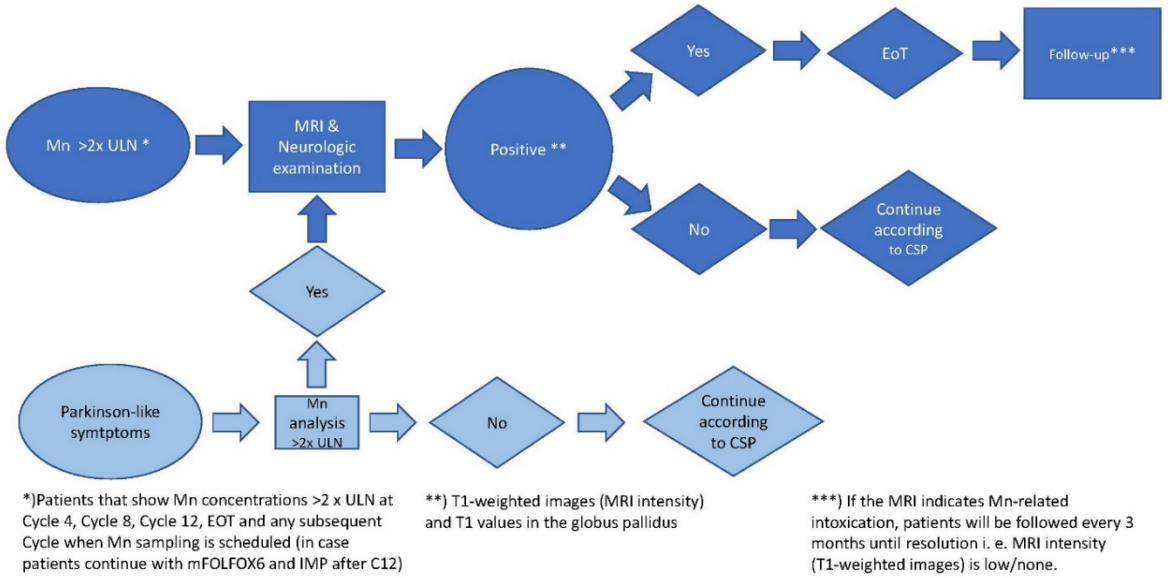
Blood for Mn assessment will be taken in the case of Parkinson-like symptoms. If the Mn level is >2 x ULN, an MRI of the brain should be performed (as above). If the Mn level is ≤2 x ULN then the patient can continue in the study according to the protocol.

However, in case of increased Mn levels, patients will be followed up at each Assessment visit throughout the study, i.e. their blood Mn level will be checked again, until resolution or the above applies.

All Mn samples must be shipped immediately for analysis by a central laboratory.

Detailed sampling and shipment instructions will be provided separately to the investigational sites.

Figure 2 Flow Chart of Monitoring Increased Mn Levels and/or Parkinson-like Symptoms



9.1.2.4 Seizures, Anaphylactoid Reactions, or Allergic Infusion Reactions

In the ongoing POLAR program, 2 patients on IMP have been reported having seizures; 1 during infusion preceding a fatal outcome and the other at 2 days after IMP infusion. One seizure has also been reported in a previous study in a patient who was treated with antiepileptics 2 days after IMP infusion. Refer to IB, Section 6 for details.

In the ongoing program there has also been 3 patients having had anaphylactoid reactions or allergic infusion reactions.

Patients with an anaphylactoid reaction/allergic infusion reaction (hypersensitivity), with moderate or severe intensity and judged to be related to IMP should discontinue dosing but still continue in the study to be followed-up.

9.1.2.5 Carcinoembryonic Antigen

Tumor marker assessments will be performed according to the Schedule of Assessments (Appendix 1).

9.1.3 Other Study Specific Parameters

9.1.3.1 Vital Signs

Vital signs will be recorded at time points according to the Schedule of Assessments (Appendix 1).

Vital signs include resting pulse (beats per minute), body temperature, and resting systolic and diastolic blood pressure and should be measured on the same arm after at least 5 minutes of supine rest.

Weight will be measured at Screening, each Treatment Visit (within 72 hours before mFOLFOX6 infusion), and the EOT visit.

Height will be recorded at Screening only.

9.1.3.2 Physical Examination

A physical examination will be performed at time points according to the Schedule of Assessments (Appendix 1).

The physical examination including a neurologic assessment (specifically including, but not limited to, tendon reflexes and sensation) should be performed according to local clinical practice prior to oxaliplatin treatment. Any abnormal/pathological findings should be recorded and judged as CS or NCS by the Investigator. Any clinically significant abnormalities should be recorded as medical history, or as AEs if started after signing ICF.

9.1.3.3 ECOG Performance Status

ECOG performance status (Table 7) will be recorded at time points according to the Schedule of Assessments (Appendix 1) and within 72 hours before mFOLFOX6 infusion.

During the COVID-19 pandemic, the ECOG Performance Status may be collected by phone or by completing the paper version of the scale that has been mailed to the patient's home, when a site visit is not feasible.

Table 7 ECOG Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 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.

* As published in Oken et al. 1982.

9.1.3.4 12-lead Electrocardiogram

No more ECGs are being done.

9.1.3.5 Tumor/Disease Assessments

Baseline radiographic assessment of disease will be performed within 42 days prior to surgery or after surgery if not done previously. The period from surgery to start of therapy should be as soon as possible, preferably within 12 weeks.

The CT or MRI scan of the thorax, abdomen and pelvis will be performed according to the Schedule of Assessments (Appendix 1) to identify any signs for CRC recurrence. The method chosen, CT (preferred) or MRI, is optional and should be in accordance with local guidelines and practice, but for each patient the same assessment should be performed throughout the study. CT/MRI scans will be read locally.

Assessment of DFS will include objective review of signs or symptoms of recurrence of CRC. Signs and symptoms may include any assessment result that, in the opinion of the Investigator, provides evidence for the recurrence of the disease, including CT or MRI, CEA, hematology, biochemistry, etc.

9.1.3.6 Brain MRI and Neurological Examination

For patients whose Mn concentrations are >2 x ULN after Cycle 4, Cycle 8, Cycle 12, EOT, and any subsequent Cycle when Mn sampling is scheduled (in case patients continue with mFOLFOX6 and IMP after Cycle 12), a brain MRI and neurological examination will be performed to evaluate any cerebral neurological impact. If the patient is NOT receiving the IMP anymore, there is no requirement to perform any brain MRI nor neurological examination.

The following assessments may be included in the neurological examination:

- Muscle strength
- Sensory and cranial nerve status
- Tendon reflexes
- Balance
- Pronation/supination hands => coordination test
- Rigidity observation (arm extension)
- Presence of tremor
- Walking test
- Bradykinesia

9.2 Appropriateness of Measurements

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology trials.

All laboratory and other assessments (pregnancy tests, vital signs, ECG, physical examination, etc.) are regarded as standard, i.e. are widely used and generally recognized as reliable, accurate and relevant.

The maximum volume of blood collected for study purposes per patient at a visit will be 20.5 mL. Details are shown in **Table 8.** Some of the assessments shown below will not be collected at all visits (see Appendix 1 for the Schedule of Assessments).

Table 8 Maximum Volume of Blood Collected for Study Purposes at a Single Visit

Assessment	Volume (mL)
CEA	0.6
Pregnancy test (serum) in WOCBP only	4.9
Hematology	4.5
Biochemistry	4.5
Mn	6.0
Total	20.5

10. STATISTICS

10.1 STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be finalized as a separate document following the global study hold and describes the technical and detailed description of the planned statistical summaries taking into account the premature study hold. The power of the study has been affected as a result of the premature stop of IMP dosing in individual patients.
For that reason the statistical analyses will be done on the combined dataset of the POLAR-A and POLAR-M studies, with data from POLAR-A and POLAR-M cohorts of patients being evaluated as separate strata.
The details of the combined and stratified analyses are layed out in the SAP..

Unless otherwise stated tabulation of summary statistics and data analysis will be performed using SAS® (Version 9.4 or later).

The Statistical Methods as originally planned are detailed below.

10.1.1 Analysis Populations

Four analysis populations will be defined:

- All patients randomized will be included in the **All Randomized Patients** population, according to their randomized treatment
- The intention to treat principle is used to define the primary analysis population, the **Full Analysis Set (FAS)**, which will consist of all randomized patients who receive at least 1 dose of the study treatment
- The **Per Protocol Set (PPS)** is defined as a subset of the FAS constituted by patients who: (a) meet all inclusion/exclusion criteria liable to affect the efficacy assessment, and (b) do not present any major protocol deviations
- The **Safety Analysis Set** will consist of all patients included in the study and treated with at least 1 dose of study treatment

10.1.2 General Considerations

Demographic and baseline characteristics (e.g. age [years], gender [male, female], race [White, Asian, Black, other], body weight [kg], height [cm], etc.), will be summarized by treatment group and overall.

Baseline characteristics and endpoints will be presented using descriptive statistics: continuous variables in terms of number of patients (n), mean, median, standard deviation (SD), and range (minimum and maximum). Categorical variables will be summarized by counts and percentages. Unless otherwise stated the calculation of proportions will be based on the sample size of the population of interest.

Missing data will be handled according to the SAP.

The primary endpoint will be analyzed only once when patients have completed and reached 12 months. Analysis of primary endpoint, major secondary endpoints and current safety data will be performed after all patients have completed treatment and reached 12 and 24 months after first dose of IMP. In addition, survival data will be analyzed after 24 months. Final evaluation and analysis of study data will be performed after all patients have completed the study.

The FAS will be primarily used in the analysis of efficacy. The primary efficacy analysis and the secondary efficacy analyses will be repeated for the PPS. The Safety Analysis Set will be considered for safety analyses.

Protocol deviations will be defined as any change, divergence, or departure from the study design or procedures. Further details will be presented in the SAP.

10.1.3 Statistical Hypothesis

The active arm will be statistically tested against placebo. For the test the statistical hypothesis is:

H0: PledOx treatment arm is equal to placebo with respect to the primary efficacy endpoint.

H1: PledOx treatment arm is not equal to placebo with respect to the primary efficacy endpoint.

For the primary endpoint, the Cochran-Mantel-Haenszel test will test the following two-sided hypothesis:

H0: $\Psi=1$ versus H1: $\Psi\neq1$

where Ψ defines the common OR of PledOx to placebo. An OR <1 favors the PledOx group.

Other secondary endpoints will be using two-sided hypothesis testing and details will be presented in the SAP.

10.1.4 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint will be analyzed using the FAS population. A summary table showing responses from all cycles, including change from baseline, will be presented by visit and treatment group.

The primary endpoint will be presented descriptively (n, %) together with its corresponding 95% CI based on the Wilson-score method and will be presented for both treatment groups. The Cochran-Mantel-Haenszel test will be performed adjusting for baseline score of FACT/GOG-NTx (2 levels) and treatment.

The OR, 95% CI and p-value using the Cochran-Mantel-Haenszel test for the difference in event rates between the 2 treatment groups will be presented. The results from the Cochran-Mantel-Haenszel test are considered the primary analysis results using the FAS.

An identical analysis, as described above, based upon the PPS will be performed.

In addition, a logistic regression analysis will be performed for the primary endpoint to adjust for treatment in the estimation of the odds. These results will be interpreted as exploratory findings.

10.1.5 Secondary Endpoint Analyses

Secondary endpoints with regard to categorical endpoints will be analyzed using the same methods as described for the primary endpoint.

Secondary endpoints with regard to continuous endpoints will be evaluated using ANCOVA, with treatment as fixed factor and baseline as a covariate.

10.1.5.1 Subgroup Analysis

A sub group analysis will be performed for categories of important prognostic factors and demography. Further details will be described in the SAP.

10.1.6 Extent of Exposure

Dosing data will be summarized by treatment group to include duration of treatment (weeks), number of patients treated by cycle, number of cycles per patient, cumulative dose, dose intensity and relative dose intensity, number (%) of patients with dose modifications (reduced or delayed), and mean duration of dose delay.

10.1.7 Safety Analysis

The safety and tolerability of PledOx/placebo is determined by reported AEs, laboratory tests, and vital signs. All safety parameters will be summarized using the Safety Analysis Set.

All AEs recorded on the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (using the most recent version). All AEs and SAEs will be summarized using descriptive statistics. The incidence and percentage of patients with at least 1 occurrence of a preferred term will be included, according to the most severe NCI CTCAE v.4.03 grade. The number of AEs reported per MedDRA preferred term will also be summarized. Causality (relationship to study therapy) will be summarized separately. Duration of AEs will be determined and included in listings along with action taken and outcome).

Laboratory results will be classified according to NCI-CTCAE v.4.03. Incidence of laboratory abnormalities will be summarized; laboratory results not corresponding to an NCI-CTCAE v.4.03 term will not be graded.

The results from physical examinations, and vital signs measurement will be tabulated. Descriptive statistics will be provided as appropriate.

10.1.7.1 Tumor/Disease Assessment, Disease Free Survival

DFS is defined as the time from the date of randomization until the date of objectively determined signs or symptoms of recurrence of 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 randomization.

Kaplan-Meier survival curves (product-limit estimates) will be presented by treatment group together with a summary of associated statistics (median survival time, 25% and 75% percentiles with their respective 95% CIs, and minimum and maximum).

The HR (including 95% CI) of PledOx compared to placebo will be calculated by Cox Proportional Hazards regression using treatment as a fixed factor in the model. A HR <1 favors the PledOx group.

These analyses will be performed on the FAS.

10.1.7.2 ECG Analysis

ECG will also be presented by listings of the major parameters (e.g. QTc).

10.1.8 Interim Analysis

No interim analysis for efficacy is planned.

10.2 SAMPLE SIZE

The primary endpoint is defined as the proportion of patients scoring 3 or 4, derived as the maximum score of items NTX 1 to 4, in any of the symptoms of numbness, tingling and discomfort in hands and feet in the FACT/GOG-NTX-13, after 9 months after the first dose.

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 randomized.

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.

10.3 LEVEL OF SIGNIFICANCE

The Type I error rate of 0.05 will be used for testing the primary and the main secondary efficacy endpoints and will be controlled using the following 3-family wise serial gatekeeping multiple comparisons procedure (MCP). Following this MCP, progression to the next family will only occur if the null hypothesis within the current family is rejected at a family-specific overall significance level. If the null hypothesis within a family is not rejected, the statistical tests corresponding to all subsequent families will be considered not statistically significant. All hypothesis tests will be 2-sided.

- The first family will include the primary endpoint: The p-value for the null hypothesis must be less than 0.05 to be considered to have met the primary efficacy objective. If the primary efficacy null hypotheses is not rejected (i.e. p-value >0.05), all subsequent statistical tests will not be considered statistically significant.

The second family will include the key secondary endpoints (see below) and they will be tested using an overall type I error rate of 0.05 by means of a hierarchical procedure, i.e. in a predefined order to control for multiplicity within this family. This will be done only if the primary endpoint has met its criteria for rejecting the null hypothesis, i.e. if $p<0.05$ for PledOx 5 µmol/kg vs placebo. Subsequently, the test for the next secondary endpoints within that family will be performed only if the preceding hypothesis test shows $p<0.05$. The predefined (hierarchical) order to test the key secondary variables will be the following:

- Proportion of patients (with mild, moderate or severe chronic CIPN) scoring 2, 3 or 4, in at least one 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 first dose of IMP.

- Mean change from baseline in sensitivity to touching cold items on day 2 of Cycle 4 of mFOLFOX6 chemotherapy, as assessed by the Cold Sensitivity questionnaire.
- Mean cumulative dose of oxaliplatin administered per patient during mFOLFOX6 chemotherapy, 9 months after the first dose of IMP.

The third family will include the remaining key secondary endpoints (see below) and they will be tested using an overall type I error rate of 0.05 by means of a (hierarchical) predefined procedure in order to control for multiplicity within this family. This will be done only if the family 1 and family 2 endpoints have met their criteria for rejecting the null hypothesis, and the order to test the remaining key secondary variables will be the following:

- Mean change from baseline in worst pain in hands or feet, using an NRS (Brief Pain Inventory short form), at 9 months after the first dose of IMP.
- Mean change from baseline in the time to complete the grooved Pegboard with the non-dominant hand, at 9 months after first dose of IMP.
- The sustained efficacy of the primary endpoint 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, 15, 18, 21 and 24 months after the first dose of IMP.

10.4 Criteria for the Termination of the Study

Refer to Sections 6.4 and 6.5.

10.5 Procedure for Accounting for Missing, Unused and Spurious 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.

There are several imputation methods used for missing values of the primary endpoint.

The first and main analysis for imputation of missing values will be done using the placebo multiple imputation method, pMI, assuming a statistical behavior of placebo- and active drug treated patients after dropout as the statistical behavior of placebo-treated patients, where missing values will be imputed based on the observed data in the placebo patients, using an imputation regression model with parameters estimated from the placebo arm (group). There will be several sensitivity analyses done for imputation of missing data.

Further details will be presented in the SAP.

10.6 Deviations from the Original Statistical Plan

Any deviations from the original statistical plan as described in this Protocol will be agreed by the Sponsor and Covance and documented and justified in an amendment, the final SAP or the final CSR, as appropriate.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The clinical monitor(s) should be given direct access to primary patient data (i.e. source data) which supports the data on the eCRFs for the study, i.e., general practice charts, hospital notes, appointment books, original laboratory records etc. Because this enters into the realm of patient confidentiality, this fact must be included in the ICF that the patient signs. Other authorized persons such as auditors may need to have direct access to this source data.

11.1 SOURCE DATA

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

11.2 SOURCE DOCUMENTS

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

11.3 DIRECT ACCESS

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party (e.g. domestic and foreign regulatory authorities, Sponsor/ Covance monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Sponsor proprietary information.

12. QUALITY CONTROL AND QUALITY ASSURANCE

An independent audit at the study site may take place at any time during or after the study. The independent audit can be carried by the Quality Assurance & Compliance (QA) Department at Covance, the QA department of the Sponsor, or a regulatory authority.

12.1 QUALITY CONTROL

Quality Control is defined as the operational techniques and activities undertaken within the QA system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

12.2 QUALITY ASSURANCE

QA is defined as the planned and systematic actions that are established to ensure that the study is performed, and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

12.2.1 Inspection

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsor's and/or Covance's facilities, or at any other establishments deemed appropriate by the regulatory authorities.

12.2.2 Audit

An Audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted, and the data were recorded, analyzed and accurately reported according to the Protocol, designated SOPs, GCP and the applicable regulatory requirements.

13. ETHICS

13.1 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in compliance with this Protocol, and in accordance with the provisions of the guidelines of the World Medical Association Declaration of Helsinki, GCP, designated SOPs, and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

The IEC/IRB must be constituted according to the local laws/guidelines.

13.2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE APPROVAL

Before initiating a study, the Investigator should have written and dated approval/favorable opinion from the relevant IRB/IEC for the study Protocol (and any amendments), written ICF, ICF updates, patient recruitment procedures (e.g. advertisements), and any other written information to be provided to patients. Approval will be indicated in writing with reference to the final Protocol number and date. Details of the IRB/IEC's constitution including names of its members and what function they perform on the committee (e.g. chairman, specialist, lay-member) should be made available to Covance.

During the study, the Investigator should provide to the IRB/IEC all documents that are patient to review.

Each participating center will submit the Protocol to the local IRB/IEC and their written, unconditional approval obtained and submitted to the Sponsor before the start of the study. Verification of the IRB/IEC's unconditional approval of the Protocol will be transmitted to the Sponsor prior to the start of the study. This approval must refer to the study by exact Protocol title and number, identify the documents reviewed and state the date of review and/or approval.

The IRB/IEC must be informed by the Investigator of all subsequent Protocol amendments and of unexpected serious adverse reactions occurring during the study which are likely to affect the safety of the patients or the conduct of the study. Approval for such changes must be transmitted in writing to the Sponsor by the Investigator.

The Investigator should provide written reports to the IRB/IEC annually or more frequently if requested on any change significantly affecting the conduct of the study and/or increasing risk to the patients. A final report of study outcome, if required, should also be submitted by the Investigator to the IRB/IEC.

13.3 INFORMED CONSENT

The principles of informed consent in the Declaration of Helsinki should be implemented in this clinical study before Protocol-specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Patients and their relatives must be given ample opportunity to inquire about details of the study.

The Investigator or designee will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information sheet. The patient will be given sufficient time to consider the study's implications before deciding whether to participate.

Consent forms must be in a language fully comprehensible to the prospective patient. Informed consent will be documented by the use of a written consent form approved by the IRB/IEC and signed by the patient and the Investigator obtaining the consent. The ICF will also be annotated with the study patient number.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. Consent must be documented by the patient's dated signature. The signature confirms the consent is based on information that has been understood. Each patient's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities and the Sponsor.

Should there be any amendments to the final Protocol, such that would directly affect the patient's participation in the study e.g. a change in any procedure, the ICF must be amended to incorporate this modification and the patient must agree to sign this amended ICF indicating that they re-consenting to participate in the study.

Patients will be instructed that they are free to obtain further information from the Investigator at any time and that they are free to withdraw their consent and discontinue participation in the study at any time without prejudice.

The prospective patient will also be advised that access to medical records would be required, and his/her general practitioner would be informed of the patient's intention to participate in this study.

13.4 MODIFICATION OF PROTOCOL

The Investigator or Covance should not implement any deviation from, or changes of, the Protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment. The only exceptions are where necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor[s], change of telephone number[s]). Non-substantial Protocol amendments may or may not be required to be submitted for approval/notification to the IRB/IECs and regulatory agencies.

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed Protocol amendment(s) should be submitted (according to national legislation):

a) To the IRB/IEC for review and approval/favorable opinion

b) To the Sponsor for agreement and, if required

c) To the regulatory authority(ies)

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the Sponsor and the Coordinating Investigator. Covance will ensure that the Investigators submit necessary Protocol amendments to the appropriate IRB/IEC.

All agreed Protocol amendments must be clearly documented using standard procedures as defined by the Sponsor, and must be signed and dated by the Sponsor and the Investigator.

14. DATA HANDLING AND RECORD KEEPING

14.1 COMPLETION OF ELECTRONIC CASE REPORT FORMS

Investigators will be provided with detailed eCRF Completion Guidelines that will identify the required data points to be collected, how to document them and when the data should be documented. Appropriate training in electronic data capture and support will be provided.

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs to record (according to the eCRF Completion Guidelines) all observations and other data pertinent to the clinical trial obtained during scheduled or unscheduled visits. All eCRFs should be fully completed to ensure accurate data interpretation.

The computerized handling of the data after receipt of the eCRFs may generate additional requests via electronic queries to which the Investigator is obliged to respond by confirming or modifying the data questioned. These requests with their responses will be appended to the eCRFs held by the Investigator and Sponsor.

The electronic data capture system is 21 CFR Part 11 compliant.

14.2 ARCHIVING

According to ICH-GCP, the documents which should be archived are ‘essential documents’ which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced.

Source documentation must also be archived. This may include observations and source data contained in medical records (certified copies or originals are acceptable for archiving purposes), data collection forms or eCRFs and research related records held in support departments. All hard copies of source documents must be retained for a period dependent on the local regulations. If electronic records of documents exist these must be backed up and retained with the hard copies.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 25 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained.

15. FINANCING AND INSURANCE

Financial disclosure information must be provided by all Investigators and Sub-Investigators and will be collected by Covance prior to the start of the study.

The sponsor holds and will maintain an adequate insurance policy covering damages arising out the study. The level of compensation will be in accordance with the country specific clinical trial insurance requirements.

16. PUBLICATION POLICY

An integrated clinical and statistical study report shall be written by PledPharma AB in consultation with the Coordinating Investigator. The results of the study may be published as an original article in an appropriate medical journal. The choice of journal will be made by PledPharma, AB with agreement from the coauthors. In a multicenter study, the first publication will be a full publication of all data from all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by Investigators or their representatives will require pre-submission review and approval by PledPharma AB.

All authors must meet at least 2 of the following criteria:

- Substantial contribution to the conception and design of the study
- Substantial contribution to the recruitment of patients (i.e., 1 of the 6 best recruiting centers within the study)
- Substantial contribution to analysis and interpretation of the data
- Substantial contribution to drafting the article or revising it critically for important intellectual content

The Coordinating Investigator(s) will be given the choice to be the first or the last author. The subsequent authors and their order will be based on scientific input to the study and recruitment (number of patients randomized and data quality). PledPharma AB will retain the right to decide on authors and to include in the authorship list names other than those of Investigators.

17. COVANCE SPECIFIC ADMINISTRATIVE PROCEDURES

17.1 STUDY PERSONNEL

Prior to the start of the study, each Investigator must supply Covance with the names and *curricula vitae* of the clinically responsible Sub-Investigators of the study and the names of other possible participants and their professional backgrounds (e.g. medical doctor, nurse, etc.).

17.2 STUDY MONITORING

The Sponsor and Covance are responsible for ensuring the proper conduct of the study with regards to Protocol adherence and validity of the data recorded on the eCRFs. Covance has therefore assigned both an Investigator and a clinical monitor to the study. With duties to aid the Investigator and at the same time, Covance, in the maintenance of complete, legible, organized and easily retrievable data. In addition, a clinical monitor will explain, interpret and ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of a pharmaceutical product and ensure an understanding of the Protocol, reporting responsibilities and the validity of the data.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data transcribed on the eCRFs and in all required reports. Data transcribed on the eCRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

17.2.1 Review of Case Report Forms

Before acceptance, the clinical monitor will review the eCRFs for completeness and adherence to the protocol.

17.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

Prior to shipment of IMP, all relevant documents must be submitted/returned to Covance by the Investigator. Refer to ICH GCP Section 8 for a list of documents.

18. REFERENCES

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19. APPENDICES

Appendix 1 **Schedule of Assessments**

Appendix 2 **FACT/GOG-NTX-13 (Version 4)**

Appendix 3 **Cold Sensitivity Patient Questionnaire**

Appendix 4 **Pain NRS Questionnaire**

Appendix 5 **EQ-5D-5L**

Appendix 6 **Study Acknowledgement / Protocol Signature Page**

Appendix 1

Schedule of Assessments: Screening, Randomization and Treatment Phase (Week 0 to Week 10)

Visit Visit Window (±2 days, if applicable)	**Screening** ≤28 days prior to start of IMP	**Rando-mization** Not a patient visit (within 3 days before Cycle 1 Day 1)	**Treatment Visit 1** Day 1, Cycle 1 Week 0 Month 0	**Treatment Visit 2** Day 1, Cycle 2 Week 2	**Treatment Visit 3** Day 1, Cycle 3 Week 4	**Treatment Visit 4** Day 1, Cycle 4 Week 6	**Treatment Visit 5** Day 1, Cycle 5 Week 8	**Treatment Visit 6** Day 1, Cycle 6 Week 10
Informed Consent	X							
Inclusion/Exclusion Criteria		X						
CT/MRI Scan and Disease Assessment[1]	X							
CEA	X (within 7 days prior to rando-mization)							
Medical History and Prior Medication	X (within 7 days prior to rando-mization)							
Physical Examination (per standard of care)	X (within 7 days prior to rando-mization)							
Vital Signs (all Visits) and Weight (only for Treatment Visits)	X (within 7 days prior to rando-mization)		X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*
* As of March 2nd., 2020, this will read as 'before mFOLFOX6 infusion'								

Visit Visit Window (±2 days, if applicable)	**Screening** ≤28 days prior to start of IMP	**Rando-mization** Not a patient visit (within 3 days before Cycle 1 Day 1)	**Treatment Visit 1** Day 1, Cycle 1 Week 0 Month 0	**Treatment Visit 2** Day 1, Cycle 2 Week 2	**Treatment Visit 3** Day 1, Cycle 3 Week 4	**Treatment Visit 4** Day 1, Cycle 4 Week 6	**Treatment Visit 5** Day 1, Cycle 5 Week 8	**Treatment Visit 6** Day 1, Cycle 6 Week 10
ECOG Performance Status	X (within 7 days prior to rando-mization)		X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*
Pregnancy Test[2]	X (within 7 days prior to rando-mization)		X before IMP infusion*		X before IMP infusion*		X before IMP infusion*	
Demographics	X (within 7 days prior to rando-mization)							
Hematology[3]	X (within 7 days prior to rando-mization)		X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*
Biochemistry[4]	X (within 7 days prior to rando-mization)		X before IMP infusion*		X before IMP infusion*		X before IMP infusion*	
Blood Mn[5]	X Sample taken within 28 days prior to first dose of IMP					X before IMP infusion*		
* As of March 2nd., 2020, this will read as 'before mFOLFOX6 infusion'								

Visit Visit Window (±2 days, if applicable)	**Screening** ≤28 days prior to start of IMP	**Rando-mization** Not a patient visit (within 3 days before Cycle 1 Day 1)	**Treatment Visit 1** Day 1, Cycle 1 Week 0 Month 0	**Treatment Visit 2** Day 1, Cycle 2 Week 2	**Treatment Visit 3** Day 1, Cycle 3 Week 4	**Treatment Visit 4** Day 1, Cycle 4 Week 6	**Treatment Visit 5** Day 1, Cycle 5 Week 8	**Treatment Visit 6** Day 1, Cycle 6 Week 10
Screening ECG (QTc)	X (within 7 days prior to rando-mization)							
Randomization[6]		X						
FACT/GOG-NTX-13[7]			X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X Before IMP infusion*	X before IMP infusion*	X before IMP infusion*
Cold Sensitivity Patient Questionnaire (Paper Diary)	X (within 7 days prior to rando-mization)			X before IMP* infusion and Days 1, 2, 3 after IMP and mFOLFOX6 infusion at Day 1		X before IMP* infusion and Days 1, 2, 3 after IMP and mFOLFOX6 infusion at Day 1		
Grooved Pegboard			X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*
Vibration Sensitivity Test (Graduated Tuning Fork)			X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*
QoL/Health Status (EQ-5D-5L)[7]			X before IMP infusion*			X before IMP infusion*		
Pain NRS[7]			X	X	X	X	X	X

Visit Visit Window (±2 days, if applicable)	**Screening** ≤28 days prior to start of IMP	**Rando-mization** Not a patient visit (within 3 days before Cycle 1 Day 1)	**Treatment Visit 1** Day 1, Cycle 1 Week 0 Month 0	**Treatment Visit 2** Day 1, Cycle 2 Week 2	**Treatment Visit 3** Day 1, Cycle 3 Week 4	**Treatment Visit 4** Day 1, Cycle 4 Week 6	**Treatment Visit 5** Day 1, Cycle 5 Week 8	**Treatment Visit 6** Day 1, Cycle 6 Week 10
			Before IMP infusion*	Before IMP infusion*	Before IMP infusion*	Before IMP infusion*	Before IMP infusion*	Before IMP infusion*
IMP (PledOx or Placebo) Administration[8]			X Only on Day 1, 15 min before chemotherapy infusion	X Only on Day 1, 15 min before chemotherapy infusion	X Only on Day 1, 15 min before chemotherapy infusion	X Only on Day 1, 15 min before chemotherapy infusion	X Only on Day 1, 15 min before chemotherapy infusion	X Only on Day 1, 15 min before chemotherapy infusion
Concomitant Medication[9]			X	X	X	X	X	X
AEs[9]	X (after signing the ICF)	X	X	X	X	X	X	X
Brain MRI and Blood Mn incl. Neurological Exam[10]			(X)[10]	(X)[10]	(X)[10]	(X)[10]	(X)[10]	(X)[10]
Health Economic Impact[12]			X before IMP infusion*					
DFS								
* As of March 2nd., 2020, this will read as 'before mFOLFOX6 infusion'								

[1] CT-scan or MRI, but the same assessment should be performed throughout the study for each patient. For screening, results from a scan performed within 42 days prior to surgery or after surgery are allowed. Tumors will be analyzed and records will be evaluated locally.

[2] WOCBP must give a negative serum pregnancy test at screening and then every 4 weeks while patient is on IMP treatment

[3] Hematology (every Treatment Visit): WBC count differential, ANC, RBC count, platelet count, and hemoglobin. Analyzed by a local hospital laboratory.

[4] Biochemistry (every 4 weeks or every 2nd Treatment Visit): ALP, total bilirubin, ALT, AST, serum creatinine, and albumin. Analyzed by a local hospital laboratory.

[5] Blood Mn (full blood): Collected at Day -28 Visit, Treatment Visit 4, 8, 12 and EOT. A patient can be enrolled without the result of Mn level analysis before the randomization, but the result should be confirmed prior to Cycle 1 Day 1. Mn samples will also be taken whenever Parkinson-like symptoms occur. Analyzed by a central laboratory.
As of March 2nd., 2020, no more Blood Mn samples will be taken with the exception for patients with Parkinson-like symptoms.

[6] Randomization (within 3 days before Cycle 1 Day 1)– this is not a patient visit. This is the moment when the Investigator will confirm that a patient complies with all inclusion/exclusion criteria and the patient will be randomized into a treatment arm using the electronic randomization system within eCRF. The Investigator will then request the unblinded pharmacist/designee to prepare the study treatment according to the randomization schedule available only to the unblinded hospital staff.

[7] Questionnaire to be completed prior to chemotherapy treatment by a patient in the hospital.
During the COVID-19 pandemic, remote data collection via either phone call or mailing of paper copies of rating scales for completion at home may be implemented.

[8] IMP (PledOx or placebo) will be administered before the background chemotherapy (mFOLFOX6). Study treatment will be stopped in case of mFOLFOX6 treatment discontinuation, disease progression, intolerable toxicity or withdrawal of consent.
As of March 2nd., 2020, the IMP administration is stopped in ongoing patients and no new patients are included in the study.

[9] All AEs including SAEs and concomitant medications will be collected up to 30 days after the last administration of IMP and AEs will be followed until resolution.
As of March 2nd.,2020, all AEs including SAEs and concomitant medications will be collected up to 30 days after the EOT visit and followed until resolution

[10] In patients who develop Parkinson-like symptoms, a neurological examination and a brain MRI will be performed and an additional blood Mn sample will be analyzed. A brain MRI and neurological examination should also be performed if elevated Mn is found during the scheduled Mn samples.

[11] If the patient continues with the study treatment until Treatment Visit 12 (Week 22), the relevant Treatment Visit or the End of Treatment Visit will be combined with the Assessment visit at Month 6. The Assessment visit at Month 6 will be performed as a separate visit only if a patient stops study treatment prior to Treatment Visit 12 (Week 22).
As of March 2nd., 2020, if the patient continues with mFOLFOX6 without IMP until Treatment Visit 12 (Week 22), the relevant Treatment Visit or End of Treatment Visit will be combined with the Assessment Visit at Month 6. The Assessment Visit of Month 6 will be performed as a separate visit only if a patient stops mFOLFOX6 prior to Treatment Visit 12 (Week 22)

[12] The Health Economic Impact Questionnaire will be completed by the Investigator or well-trained site staff.
During the COVID-19 pandemic, remote data collection via either phone call or mailing of rating scales for completion at home may be implemented for the Health Economic Impact Questionnaire.

Schedule of Assessments: Treatment Phase (Month 3 to Month ≥6) and End of Treatment Visit

Visit Visit Window (±2 days, if applicable)	**Assessment Visit** Month 3	**Treatment Visit 7** Day 1, Cycle 7 Week 12	**Treatment Visit 8** Day 1, Cycle 8 Week 14	**Treatment Visit 9** Day 1, Cycle 9 Week 16	**Treatment Visit 10** Day 1, Cycle 10 Week 18	**Treatment Visit 11** Day 1, Cycle 11 Week 20	**Treatment Visit 12** Day 1, Cycle 12 Week 22	**Assessment Visit** Month 6[11]	**EOT Visit** Day 14 Cycle 12 (or Last Cycle if before Cycle 12) (±3 days)
Informed Consent									
Inclusion/Exclusion Criteria									
CT/MRI Scan and Disease Assessment[1]									
CEA									X
Medical History and Prior Medication									
Physical Examination (per Standard of Care)	X							X	X
Vital Signs (all Visits) and Weight (only for Treatment Visits and EOT visit)	X	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X	X
ECOG Performance Status	X	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X	X
Pregnancy Test[2]		X before IMP infusion*		X before IMP infusion*		X before IMP infusion*			X
Demographics									

Visit Visit Window (±2 days, if applicable)	**Assessment Visit** Month 3	**Treatment Visit 7** Day 1, Cycle 7 Week 12	**Treatment Visit 8** Day 1, Cycle 8 Week 14	**Treatment Visit 9** Day 1, Cycle 9 Week 16	**Treatment Visit 10** Day 1, Cycle 10 Week 18	**Treatment Visit 11** Day 1, Cycle 11 Week 20	**Treatment Visit 12** Day 1, Cycle 12 Week 22	**Assessment Visit** Month 6[11]	**EOT Visit** Day 14 Cycle 12 (or Last Cycle if before Cycle 12) (±3 days)
Hematology[3]	X	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X	X
Biochemistry[4]		X before IMP infusion*		X before IMP infusion*		X before IMP infusion*			X
Blood Mn[5]			X before IMP infusion*				X before IMP infusion*		X
Screening ECG (QTc)									
Randomization[6]									
FACT/GOG-NTX-13[7]	X	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X	X
Cold Sensitivity Patient Questionnaire (Paper Diary)			X before IMP* infusion and Days 1, 2, 3 after IMP and mFOLFOX6 infusion at Day 1						
Grooved Pegboard	X	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X	X
* As of March 2nd., 2020, this will read as 'before mFOLFOX6 infusion'									

Visit Visit Window (±2 days, if applicable)	**Assessment Visit** Month 3	**Treatment Visit 7** Day 1, Cycle 7 Week 12	**Treatment Visit 8** Day 1, Cycle 8 Week 14	**Treatment Visit 9** Day 1, Cycle 9 Week 16	**Treatment Visit 10** Day 1, Cycle 10 Week 18	**Treatment Visit 11** Day 1, Cycle 11 Week 20	**Treatment Visit 12** Day 1, Cycle 12 Week 22	**Assessment Visit** Month 6[11]	**EOT Visit** Day 14 Cycle 12 (or Last Cycle if before Cycle 12) (±3 days)
Vibration Sensitivity Test (Graduated Tuning Fork)	X	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X	X
QoL/Health Status (EQ-5D-5L) [7]	X		X before IMP infusion*				X before IMP infusion*	X	X
Pain NRS[7]	X	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X before IMP infusion*	X	X
IMP (PledOx or Placebo) Administration[8]		X 15 min before chemotherapy infusion only on Day 1	X 15 min before chemotherapy infusion only on Day 1	X 15 min before chemotherapy infusion only on Day 1	X 15 min before chemotherapy infusion only on Day 1	X 15 min before chemotherapy infusion only on Day 1	X 15 min before chemotherapy infusion only on Day 1		
Concomitant Medication[9]	X	X	X	X	X	X	X	X	X
AEs[9]	X	X	X	X	X	X	X	X	X
Brain MRI and Blood Mn incl. Neurological Exam[10]	(X)[10]	(X)[10]	(X)[10]	(X)[10]	(X)[10]	(X)[10]	(X)[10]		(X)[10]
Health Economic Impact[12]								X	
DFS	X							X	
* As of March 2nd., 2020, this will read as 'before mFOLFOX6 infusion'									

[1] CT-scan or MRI, but the same assessment should be performed throughout the study for each patient. Tumors will be analyzed and the records will be evaluated locally.
[2] WOCBP must give a negative serum pregnancy test at screening and then every 4 weeks while patient is on IMP treatment.
[3] Hematology (every Treatment Visit): WBC count differential, ANC, RBC count, platelet count, and hemoglobin. Analyzed by a local hospital laboratory.

[4] Biochemistry (every 4 weeks or every 2nd Treatment Visit): ALP, total bilirubin, ALT, AST, serum creatinine, and albumin. Analyzed by a local hospital laboratory.

[5] Blood Mn (full blood): Collected at Day -28 Visit, Treatment Visit 4, 8, 12 and EOT. A patient can be enrolled without the result of Mn level analysis before the randomization, but the result should be confirmed prior to Cycle 1 Day 1. Mn samples will also be taken whenever Parkinson-like symptoms occur. Analyzed by a central laboratory.
As of March 2nd., 2020, no more Blood Mn samples will be taken with the exception for patients with Parkinson-like symptoms.

[6] Randomization (within 3 days before Cycle 1 Day 1)– this is not a patient visit. This is the moment when the Investigator will confirm that a patient complies with all inclusion/exclusion criteria and the patient will be randomized into a treatment arm using the electronic randomization system within eCRF. The Investigator will then request the unblinded pharmacist/designee to prepare the study treatment according to the randomization schedule available only to the unblinded hospital staff.

[7] Questionnaire to be completed prior to chemotherapy treatment by a patient in the hospital.
During the COVID-19 pandemic, remote data collection via either phone call or mailing of rating scales for completion at home may be implemented.

[8] IMP (PledOx or placebo) will be administered before the background chemotherapy (mFOLFOX6). Study treatment will be stopped in case of mFOLFOX6 treatment discontinuation, disease progression, intolerable toxicity or withdrawal of consent.
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[12] The Health Economic Impact Questionnaire will be completed by the Investigator or well-trained site staff.
During the COVID-19 pandemic, remote data collection via either phone call or mailing of rating scales for completion at home may be implemented.

Schedule of Assessments: Follow-up Phase (Month 9 to Month 24 [EOS])

Visit Visit Window (±1 week)	**Assessment Visit** Month 9	**Assessment Visit** Month 12	**Assessment Visit** Month 18	**EOS Visit** Month 24
Informed Consent				
Inclusion/Exclusion Criteria				
CT/MRI Scan and Disease Assessment[1]		X		X
CEA		X		X
Medical History and Prior Medication				
Physical Examination (per Standard of Care)	X	X	X	X
Vital Signs (all Visits) and Weight (only for Treatment Visit)	X	X	X	X
ECOG Performance Status	X	X	X	X
Pregnancy Test[2]				
Demographics				
Hematology[3]				
Biochemistry[4]				
Blood Mn[5]				
Screening ECG (QTc)				
Randomization[6]				
FACT/GOG-NTX-13[7]	X	X	X	X
Cold Sensitivity Patient Questionnaire (Paper Diary)				

Visit Visit Window (±1 week)	**Assessment Visit** Month 9	**Assessment Visit** Month 12	**Assessment Visit** Month 18	**EOS Visit** Month 24
Grooved Pegboard	X	X	X	X
Vibration Sensitivity Test (Graduated Tuning Fork)	X	X	X	X
QoL/Health Status[7] (EQ-5D-5L)	X	X	X	X
Pain NRS[7]	X	X	X	X
IMP (PledOx or Placebo) Administration[8]				
Concomitant Medication[9]				
AEs[9]				
Brain MRI and Blood Mn incl. Neurological Exam[10]				
Health Economic Impact[12]		X	X	X
DFS	X	X	X	X

[1] CT-scan or MRI, but the same assessment should be performed throughout the study for each patient. Tumors will be analyzed and the records will be evaluated locally.

[2] WOCBP must give a negative serum pregnancy test at screening and then every 4 weeks while patient is on IMP treatment.

[3] Hematology (every Treatment Visit): WBC count differential, ANC, RBC count, platelet count, and hemoglobin. Analyzed by a local hospital laboratory.

[4] Biochemistry (every 4 weeks or every 2nd Treatment Visit): ALP, total bilirubin, ALT, AST, serum creatinine, and albumin. Analyzed by a local hospital laboratory.

[5] Blood Mn (full blood): Collected at Day -28 Visit, Treatment Visit 4, 8, 12 and EOT. A patient can be enrolled without the result of Mn level analysis before the randomization, but the result should be confirmed prior to Cycle 1 Day 1. Mn samples will also be taken whenever Parkinson-like symptoms occur. Analyzed by a central laboratory.
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[7] Questionnaire to be completed prior to chemotherapy treatment by a patient in the hospital.
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[8] IMP (PledOx or placebo) will be administered before the background chemotherapy (mFOLFOX6). Study treatment will be stopped in case of mFOLFOX6 treatment discontinuation, disease progression, intolerable toxicity or withdrawal of consent.
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During the COVID-19 pandemic, remote data collection via either phone call or mailing of paper copies of rating scales for completion at home may be implemented for the Health Economic Impact Questionnaire.

Appendix 2

FACT/GOG-NTX-13 (Version 4)

FACT/GOG-NTX-13 (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

English (Universal)

16 November 2007
Page 1 of 3

FACT/GOG-NTX-13 (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT/GOG-NTX-13 (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
NTX 10	I have pain in my hands or feet when I am exposed to cold temperatures	0	1	2	3	4
NTX 11	I have difficulty breathing when I am exposed to cold temperatures	0	1	2	3	4

Appendix 3

Cold Sensitivity Patient Questionnaire

1. **Did you experience sensitivity to touching cold items within the last 24 hours?**

Not at all										As bad as it can be
0	1	2	3	4	5	6	7	8	9	10

2. **Did you experience discomfort swallowing cold liquids within the last 24 hours?**

Not at all										As bad as it can be
0	1	2	3	4	5	6	7	8	9	10

3. **Did you notice any throat discomfort within the last 24 hours?**

Not at all										As bad as it can be
0	1	2	3	4	5	6	7	8	9	10

4. **Did you suffer from muscle cramps within the last 24 hours?**

Not at all										As bad as it can be
0	1	2	3	4	5	6	7	8	9	10

Appendix 4

Pain Numerical Rating Scale (NRS) Questions

During the past week, have you experienced any pain in your hands or feet?
Yes ☐ No ☐

If yes, answer the following three questions;

1. Please rate your pain by circling the number that best describes your pain at its worst in last 7 days.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

2. Please rate your pain by circling the number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

3. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Appendix 5

EQ-5D-5L

https://euroqol.org/wp-content/uploads/2016/10/Sample_UK__English__EQ-5D-5L_Paper_Self_complete_v1.0__ID_24700.pdf

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

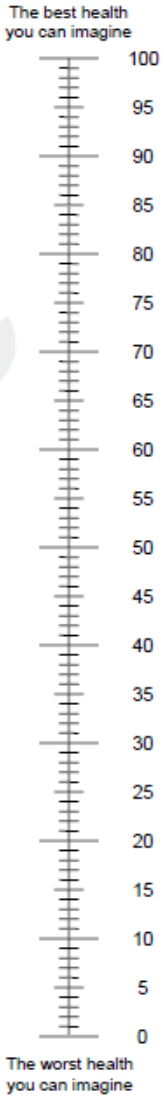
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix 6

STUDY ACKNOWLEDGEMENT / PROTOCOL SIGNATURE PAGE

Investigator's Statement:

I have read and understand the foregoing Protocol entitled "A Phase 3, double-blind, multicenter, placebo-controlled study of PledOx used on top of Modified FOLFOX6 (5-FU/FA and Oxaliplatin) to prevent chemotherapy induced peripheral neuropathy (CIPN) in the adjuvant treatment of patients with Stage III or high-risk Stage II colorectal cancer", protocol number PP06489 (POLAR-A), and agree to conduct the study in compliance with Good Clinical Practice (CPMP/ICH/135/95), ICH GCP, designated standard operating procedures, national laws and regulations of the countries conducting the study and within the principles of the Declaration of Helsinki as outlined herein.

Investigator's Name (please print)	Investigator's Title
Date (dd mmm yyyy)	Investigator's Signature