PROTOCOL TITLE: An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas

STUDY PROTOCOL

STUDY NUMBER: D-US-60010-001

Irinotecan liposome injection (IPN60010)

EudraCT number: 2018-003585-14

ClinicalTrials.gov number: NCT04083235.

Version 5.0 (with Amendment 4): 19 August 2021

Study Sponsor:

Ipsen Bioscience, Ipsen Group

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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol D-US-60010-001 entitled 'An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.' I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: [ ]
TITLE: [PRINCIPAL] INVESTIGATOR SIGNATURE:

DATE:
OFFICE: [ ]
[ ]
[ ]
[ ]
[ ]

Sponsor's Representative Signature:
NAME: PPD
TITLE: PPD SIGNATURE:

DATE:
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650 East Kendal Street
Cambridge, Massachusetts 02142
USA

COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol D-US-60010-001 entitled 'An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.' I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: COORDINATING INVESTIGATOR SIGNATURE:

DATE:

OFFICE: [ ]
[ ]
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SUMMARY OF CHANGES

The initial version of the protocol dated 03 October 2019 was amended four times. The current version of the protocol was released on 19 August 2021 and includes all amendments (see Table 1).

All changes from the United Kingdom (25 February 2020) and Germany (27 March 2020) protocol addenda produced in response to the country-specific requests from the regulatory authorities received during the clinical trial submission process were included in the protocol version 3.0 (amendment 2).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	28 November 2019	Appendix 9
2	20 May 2020	Appendix 10
3	03 June 2020	Appendix 11
4	19 August 2021	Appendix 12

SYNOPSIS

Name of sponsor/company: Ipsen Bioscience	
Name of finished product: Irinotecan liposome injection **Name of active ingredient(s)**: Irinotecan in the form of sucrosofate salt	
Title of study: An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas. **Study number**: D-US-60010-001	
Number of planned centres: approximately 200 to 245 sites worldwide	
Planned study period: The study will be completed once all subjects have died, withdrawn consent or are lost to follow-up.	**Phase of development**: Phase III
Study type: interventional, open-label, randomised, multicentre, efficacy and safety study	

Study Objectives:

Primary Objective:

The primary objective of this study is to evaluate the efficacy of the regimen of irinotecan liposome injection + oxaliplatin + 5-fluorouracil (5-FU)/leucovorin (LV) versus nab-paclitaxel + gemcitabine in improving overall survival (OS) in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

Secondary Objectives:

The secondary objectives of this study are as follows:

- To evaluate progression free survival (PFS) according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 guidelines
- To evaluate the overall response rate (ORR) according to RECIST Version 1.1 guidelines
- To evaluate the safety of this regimen in this patient population.

Exploratory Objectives:

- To evaluate time to deterioration or worsening of subjects physical functioning, disease related symptoms and treatment related symptoms of interest using patient-reported outcome (PRO) data collected using the European Organisation for Research and Treatment of Cancer quality-of-life-core questionnaire (EORTC QLQ-C30), specific pancreatic cancer module (QLQ-PAN26) questionnaire and PRO of Common Terminology Criteria of Adverse Events (PRO-CTCAE) as well as the EuroQol 5 dimension health status questionnaire (5 level) (EQ-5D-5L).
- To evaluate the pharmacokinetics (PK), and the relationship between PK exposure and efficacy and safety, of the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV (Arm 1) in this patient population
- To compare time to treatment failure (TTF) between treatment arms
- To compare duration of response (DOR) between treatment arms
- To compare time to response (TTR) between treatment arms

- To describe the possible association between genotypes to include but not be limited to UGT1A1*28 and other UGT1A genotypes, SN-38 concentration (only for subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV) and safety
- To explore the pharmacodynamic biomarker CA 19-9 for the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV compared with nab-paclitaxel+gemcitabine in this patient population.
- To conduct biobanking of samples for future analysis of biomarkers amongst subjects who consent to optional biobanking.
- To collect gene mutation and genomic alteration status associated with pancreatic adenocarcinoma of subjects determined prior to screening (if available).

Study hypothesis: Irinotecan liposome injection+oxaliplatin+5-FU/LV has superior efficacy over nab-paclitaxel+gemcitabine, demonstrated by a 3-month improvement in OS, in the treatment of subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

Methodology:

This is an open-label, randomised, multicentre, phase III study. Subjects will be randomised in a 1:1 ratio to one of the following treatment regimens:

- Arm 1: irinotecan liposome injection+oxaliplatin+5-FU/LV
- Arm 2: nab-paclitaxel+gemcitabine

There is no pre-defined duration of treatment for each subject. It is intended that subjects will be treated until radiologically determined progressive disease per RECIST Version 1.1, unacceptable study medication related toxicity or withdrawal from study.

Number of subjects planned:

Approximately 750 subjects are planned to be randomised (approximately 375 subjects per arm).

Diagnosis and criteria for inclusion:

Inclusion criteria:

A subject will be eligible for inclusion in this study only if all the following criteria are met:

General inclusion criteria

(1) Subject has been informed about the nature of the study, and has agreed to participate in the study, and signed the informed consent form (ICF) prior to participation in any study-related activities.

(2b) Male or non-pregnant and non-lactating female and ≥18 years of age:

(a) Females of child-bearing potential (i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy) must test negative for pregnancy at the time of screening based on a urine or serum pregnancy test. 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 postmenopausal 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. Female subjects of reproductive potential must agree to use a highly effective method of birth

control, during the study and for 7 months following the last dose of study medication (see also Appendix 4 and Section 4.3.3).

(b) Male subjects must agree to use condoms during the study and for 6 months following the last dose of study medication.

Disease specific inclusion criteria

(3) Histological or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting.

(4) Initial diagnosis of metastatic disease (as per American Joint Committee on Cancer 8th Edition [AJCC 2017]) must have occurred ≤6 weeks prior to screening.

(5a) Subject has one or more metastatic lesions measurable by computed tomography (CT) scan (or magnetic resonance imaging (MRI), if the subject is allergic to CT contrast media) according to RECIST Version 1.1 criteria.

(6a) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening and within 7 days prior to randomisation.

Haematological, biochemical and organ function inclusion criteria

(7a) Subject has adequate biological parameters as demonstrated by the following blood counts:

(a) Absolute neutrophil count (ANC) ≥2000/mm^3 without the use of hemopoietic growth factors within the last 7 days prior to randomisation

(b) Platelet count ≥100,000/mm^3

(c) Haemoglobin (Hgb) ≥9 g/dL obtained ≤14 days prior to randomisation.

(8) Adequate hepatic function as evidenced by:

(a) Serum total bilirubin ≤1.5x upper limit of normal (ULN) (biliary drainage is allowed for biliary obstruction), and

(b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5x ULN (≤5x ULN is acceptable if liver metastases are present).

(9) Adequate renal function with a creatinine clearance (CL_{CR}) of >30 mL/min. Actual body weight should be used for calculating CL_{CR} using the Cockcroft-Gault Equation: CL_{CR} (mL/min) = ((140–Age [years]) * (Weight [kg]/(Serum Creatinine [mg/dL]*72). Multiply the result by 0.85 if the subject is female. For subjects with a body mass index (BMI) >30 kg/m^2, adjusted body weight should be used instead.

(10a) Electrocardiogram (ECG) without any clinically significant findings (QT interval corrected by Fridericia's formula (QTcF) ≤450 msec and no known arrhythmias) and per the investigator's assessment.

(11) Adequate coagulation studies (obtained ≤14 days prior to randomisation) as demonstrated by prothrombin time and partial thromboplastin time within normal limits (≤1.5 x ULN). (Subjects on warfarin or other vitamin K antagonists should be discussed with the sponsor).

(12) Subject has no clinically significant abnormalities in urinalysis results (obtained within the last 7 days prior to randomisation), per the investigator's assessment.

(13) Subjects infected with human immunodeficiency virus (HIV) are eligible if they meet all the following criteria:

(a) CD4 count is ≥350 cells/uL, viral load is undetectable, and not taking prohibited cytochrome (CYP)-interacting medications

(b) Probable long-term survival with HIV if cancer were not present

(c) Stable on a highly active antiretroviral therapy (HAART) regimen for ≥4 weeks and willing to adhere to their HAART regimen with minimal overlapping toxicity and drug-drug interactions with the experimental agents in this study

(d) HIV is not multi-drug resistant

(e) Taking medication and/or receiving antiretroviral therapy that does not interact or have overlapping toxicities with the study medication.

***Exclusion criteria*:**

Subjects must meet all the inclusion criteria listed above and none of the following exclusion criteria:

General exclusion criteria

(1) Any other medical or social condition deemed by the investigator to be likely to interfere with a subject's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.

(2a) Unwilling or unable to comply with study procedures and/or study visits, including long-term follow-up for survival.

Disease specific exclusion criteria

(3) Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy:

(a) Palliative radiotherapy is permitted

(b) Placement of biliary stent/tube is permitted.

(4) Prior treatment of pancreatic adenocarcinoma with chemotherapy in the adjuvant setting, except those where at least 12 months have elapsed since completion of the last dose and no persistent treatment-related toxicities are present.

(5) Subject has only localised advanced disease.

(6a) Documented serum albumin <3 g/dL within 7 days prior to randomisation.

(7) Known history of central nervous system (CNS) metastases. (Subjects on a stable or decreasing dose of steroids and deemed clinically stable as per the investigator's assessment are eligible).

(8) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, diarrhoea >Grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease or partial bowel obstruction.

(9) History of any second malignancy in the last 2 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Subjects with a history of other malignancies are eligible if they have been continuously disease free for at least 2 years prior to screening. Subjects who have a concurrent malignancy that is clinically stable and does not require tumour-directed treatment are eligible.

Haematological, biochemical and organ function exclusion criteria

(10) Known hypersensitivity to any of the components of irinotecan liposome injection, other liposomal products, or any components of 5-FU, LV or oxaliplatin.

(11) Known hypersensitivity to any of the components of nab-paclitaxel or gemcitabine.

(12) Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including:

(a) Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening

(b) High cardiovascular risk, including, but not limited to, recent coronary stenting or myocardial infarction in the past year prior to screening

(c) New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure

(d) Known historical or active infection with hepatitis B, or active infection with hepatitis C (note that subjects with hepatitis C who have been clinically cured, defined as persistent absence of hepatitis C ribonucleic acid (RNA) detected by polymerase chain reaction (PCR) test in serum 12 weeks after completing antiviral treatment, are eligible for this study)

(13) Active infection or an unexplained fever >38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, subjects with tumour fever may be enrolled), which in the investigator's opinion might compromise the subject's participation in the study or affect the study outcome.

(14) Major surgery, other than diagnostic surgery, within 4 weeks prior to randomisation.

(15) Use of strong inhibitors or inducers of CYP3A, CYP2C8 and UGT1A1 (please refer to Appendix 1). Subjects are ineligible if:

- they are unable to discontinue the use of strong inhibitors of CYP3A, CYP2C8 and UGT1A1 at least 1 week prior to randomisation
- they are unable to discontinue the use of strong CYP3A and CYP2C8 inducers at least 2 weeks prior to randomisation.

(16) There is presence of any contraindications outlined in the Contraindications or Warnings and Precautions sections of the investigator brochure (IB) for irinotecan liposome injection, or in the prescribing information for 5-FU, LV or oxaliplatin.

(17) There is presence of any contraindications outlined in the Contraindications or Special Warnings and Precautions sections of the product prescribing information for nab-paclitaxel or gemcitabine.

(18) Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma.

(19) Subjects who, in the opinion of the investigator, have symptoms or signs suggestive of clinically unacceptable deterioration of the primary disease at the time of screening.

(20a) History of systemic connective tissue disorders (e.g. lupus, scleroderma, arteritis nodosa).

(21) History of interstitial lung disease, history of slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.

(22) History of peripheral artery disease (e.g. claudication, Leo Buerger's disease).

(23) Subjects who have received a live vaccine within 4 weeks prior to randomisation.

(24) Known low or absent dihydropyrimidine dehydrogenase (DPD) activity. Where required by local regulations, testing for DPD deficiency must be performed using a validated method which is recommended by local health authorities.

Test product, dose and mode of administration:

Irinotecan liposome injection (also known as Nal-IRI, BAX2398, PEP02, liposomal irinotecan and MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous (i.v.) infusion. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrosofate salt. It is supplied in sterile, single-use vials containing 10 mL of liposome irinotecan injection at a concentration of 4.3 mg/mL free base equivalent (FBE). Irinotecan liposome injection must be stored refrigerated (2 to 8°C, 36 to 46°F) with protection from light and must not be frozen.

Irinotecan liposome injection dose will be expressed as FBE.

The test product irinotecan liposome injection is administered in combination with oxaliplatin and 5-FU/LV.

Arm 1: Doses and administration of irinotecan liposome injection, oxaliplatin, 5-FU/LV, on Days 1 and 15 of each 28-day cycle will be:

- Irinotecan liposome injection administered at 50 mg/m^2 (FBE) i.v. over 90 minutes (±10 minutes)
- Oxaliplatin administered at 60 mg/m^2 i.v. over 120 minutes (±10 minutes)
- LV (l+d racemic form-generic form) 400 mg/m^2, i.v. over 30 minutes (±5 minutes)
- 5-FU administered 2400 mg/m^2 i.v. over 46-hours (±120 minutes)

Dose level reductions required due to toxicity related to irinotecan liposome injection, oxaliplatin, LV and 5-FU should be made following the guidelines outlined in Appendix 2.

Reference therapy, dose and mode of administration:

Arm 2: Doses and administration of nab-paclitaxel and gemcitabine and on Days 1, 8 and 15 of each 28-day cycle will be:

- Nab-paclitaxel administered at 125 mg/m^2 i.v. over 35 minutes (±5 minutes)
- Gemcitabine administered at 1000 mg/m^2 i.v. over 30 minutes (±5 minutes)

Dose level reductions required due to toxicity related to nab-paclitaxel and gemcitabine should be made following the guidelines outlined in Appendix 3.

Duration of treatment:

Both regimens are 28-day cycles unless cycle duration is modified by toxicity.

The toxicity of each dose must be recorded prior to the administration of a subsequent dose and graded according to the National Cancer Institute (NCI) CTCAE (Version 5.0). All dose modifications for all arms should be based on the worst preceding toxicity.

Dosing may be delayed to allow for recovery from toxicity related to the study treatment. If the time required for recovery from toxicity is more than 14 days in Arm 1 or 21 days in Arm 2, consideration should be given to discontinuing the subject from further treatment, unless the subject is demonstrating benefit overall, in which case the possibility of remaining on study medication should be discussed between investigator and sponsor, after review of the associated risks and benefits. However, if oxaliplatin is not well tolerated in subjects randomised to Arm 1, oxaliplatin may be discontinued and subjects may continue to receive irinotecan liposome injection+5-FU/LV at the discretion of the investigator and continue in the study.

If a subject's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation is not permitted (with exception, see Appendix 3). In Arm 1 any subject who has three dose reductions and experiences an adverse

event (AE) that would require a fourth dose reduction must be discontinued from study treatment. In Arm 2, any subject who has two dose reductions and experiences an AE that would require a third dose reduction must be discontinued from study treatment. Toxicity requiring discontinuation of any of the drugs in either regimen (apart from oxaliplatin) will result in discontinuation from the study treatment.

A subject who discontinues study medication and has not withdrawn from the study must continue with all ongoing protocol requirements until confirmed radiographic disease progression or until the start of alternative anti-cancer therapy.

A follow-up clinic visit is required approximately 30 days after last dose of study treatment to complete the final safety assessments. Subsequently, subjects will be followed for survival once every 2 months via telephone, email, or clinic visit until death or study closure, whichever occurs first.

Criteria for evaluation (endpoints):

Primary and Key Secondary Efficacy Endpoints and main evaluations:

Efficacy Assessments

Subjects will have CT scans (or MRI if the subject is allergic to CT contrast media) performed every 8 weeks that will be evaluated by the investigator site using RECIST guidelines Version 1.1 for complete response, partial response, stable disease or progressive disease.

Subjects will be followed in the study until death to assess OS time. Subjects who have terminated study medication treatment will have follow-up every 2 months to determine survival status.

Efficacy:

Primary Endpoint(s) and Evaluation(s):

Primary Efficacy

The primary efficacy endpoint is the OS of subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV compared to subjects treated with nab-paclitaxel+gemcitabine.

Secondary Endpoints(s) and Evaluation(s):

Secondary Efficacy

The secondary efficacy endpoints (PFS and ORR) will only be evaluated if the primary efficacy endpoint demonstrates superiority for irinotecan liposome injection+oxaliplatin+5-FU/LV over nab-paclitaxel+gemcitabine. Investigator-assessed tumour response will be used in efficacy analysis.

Pharmacokinetics:

Plasma concentrations of total irinotecan and SN-38 will be used to characterise their corresponding PK parameters, in co-administration with 5-FU and oxaliplatin, using a nonlinear mixed effects approach. Individual PK parameters will be estimated if warranted by the data. Oxaliplatin and/or 5-FU concentrations might be used for further PK characterisation if more investigations are required.

Graphical exploration will be performed to investigate any relationship between PK and PD endpoints. If a trend is shown, PK/PD modelling will be performed and reported separately.

Safety:

Safety will be monitored through continuous reporting of AEs and serious adverse events (SAEs), laboratory abnormalities, and incidence of subjects experiencing dose modifications (including dose reductions, dose omissions and dose delays) and/or premature discontinuation of study medication (and reason for discontinuation).

The safety evaluations include:

- AEs
- Clinical laboratory assessments
- ECG findings
- Complete physical examination including the evaluation of ECOG, vital signs, measurements and body weight.

These safety evaluations will be performed from ICF signature, throughout the study to 30 days after the last study treatment administration.

An independent data and monitoring committee (IDMC) will be established for this study to operate as an independent expert advisory group with the primary responsibility of monitoring the safety of enrolled subjects by reviewing the clinical data at scheduled time points described in the IDMC Charter, as well as on an ad hoc basis, as needed. The IDMC will additionally review the safety and efficacy of the interim analysis and make appropriate recommendations based on those results.

Statistical Methods:

Method of Randomisation:

- Randomisation ratio 1:1
- Stratification factors:
  - ECOG Performance Status (0 or 1)
  - Region (North America/East Asia/Rest of the World)
  - Liver metastases (Yes/No)

Sample Size and Power Considerations:

The study sample size required to demonstrate an improvement in OS of irinotecan liposome injection+oxaliplatin+5-FU/LV compared with nab-paclitaxel+gemcitabine has been calculated using the following assumptions:

- expected median OS on nab-paclitaxel+gemcitabine arm of 9 months
- expected median OS on irinotecan liposome injection+oxaliplatin+5-FU/LV arm of 12 months
- for detection of a true HR of 0.75
- one-sided test
- overall type I error rate = 0.025
- power = 90%
- randomisation allocation ratio 1:1 (Arm 1: Arm 2).

Approximately 750 subjects will be randomised in a 1:1 ratio to the two treatment arms. Accounting for the planned interim analysis, follow-up until at least 543 OS events are observed across the two treatment arms provide at least 90% power to detect a true HR $\leq$0.75 (modified OS: 9 versus 12 months), using a stratified log-rank test with overall 1-sided significance level of 0.025 (adjusted for interim analysis).

Assuming enrolment over 16 months increasing to approximately 62 subjects per month and lost-to-follow-up rate of 5% across both treatment arms, the timing of the interim analysis is expected to be at 24 months after the first subject treated and the timing of the final analysis is expected to be at 36.5 months after the first subject treated.

If blinded projection of the accumulating OS events suggests that the number required for the final analysis will not be reached (due to censoring) within 32 months of study initiation,

the sample size may be increased up to 800 subjects or until prespecified events are met, whichever comes earlier. The projection to inform the decision to potentially increase the number of subjects will be carried out within 3 months prior to expected completion of planned enrolment of 750 subjects.

Primary Efficacy Analyses

The final analysis will be performed using the intention to treat (ITT) population. The OS for each treatment arm will be summarised by median survival time (including 95% confidence intervals (CI)) from Kaplan-Meier estimation. The Kaplan-Meier curve for survival will be presented for each treatment arm. Stratified analyses based on the randomisation stratification factors from the IWRS data will be used for treatment comparisons. Differences in the OS curves will be tested using a stratified log-rank test. The estimated treatment effect for Arm 1 will be summarised by the HR (including 95% CI) from stratified Cox regression analysis.

There are two planned analyses of OS: interim analysis and final analysis. The interim analysis is planned when at least 272 OS events (i.e. 50% information time) have been observed in the ITT population. If that analysis does not indicate futility or efficacy, then the final analysis is planned at 543 OS events when 100% of the planned number of subjects have been enrolled. The overall type I error is controlled at 1-sided significance level of 0.025 (adjusted for interim analysis). To control type I and type II errors, the planned interim analysis will utilise Hwang-Shi-Decani (HSD) alpha and (non-binding) beta spending function with γ parameter equal to -4 for type I error type and γ equal to -1 for type II error. If interim analysis does not indicate futility or efficacy, the final analysis is planned when 543 OS events are observed.

Secondary Efficacy Analyses

Secondary efficacy endpoints will be tested no more than once. If the primary endpoint of OS is declared significant at the interim analysis, secondary efficacy endpoints will be tested at the interim; otherwise at the final analysis if OS is found to be statistically significant at that analysis. Hypothesis testing of secondary efficacy endpoints will be conducted in a stagewise hierarchical manner incorporating alpha spending for each endpoint using HSD γ_{alpha}= -4, similar to that specified for the primary efficacy analysis. The nominal level for the comparison will depend on whether the analysis is carried out at the OS interim or at the planned OS final analysis.

The first endpoint in the hierarchy of secondary endpoints will be PFS. If OS and PFS are both significant, then ORR would be tested. Any parameter which is not formally tested for significance (per the hierarchy) will be regarded as descriptive and exploratory.

Safety Analyses

Safety analyses will be performed using the safety population. All safety data will be included in the subject data listings.

Tabular summaries will present incidence by treatment arm for all treatment-emergent adverse events (TEAEs), SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to death, TEAEs related to study medications. All the safety data will be described by grade (all grades and Grade 3 and higher). All events will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or later by system organ class and preferred term.

Laboratory data will be presented by treatment arm. Abnormal laboratory values will be assessed using all available tests results and toxicity grading will be assigned according to NCI CTCAE (Version 5.0) toxicity scale, where criteria are available to do so. Laboratory, vital signs, and ECG data will be summarised according to parameter type.

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
5-FU	5-fluorouracil
ACS	American Cancer Society
AE	Adverse event
AESI	Adverse events of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARID1A	AT-Rich Interaction Domain 1A gene
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC_{Tau}	Area under the concentration time curve over the dosing interval
BMI	Body mass index
BOR	Best overall response
BRCA 1	Breast Cancer 1 gene
BRCA 2	Breast Cancer 2 gene
BSA	Body surface area
C#D#	Cycle #, Day #
CA	Competent Authority
CA19-9	Carbohydrate antigen 19.9
CDKN2	Cyclin-Dependent Kinase inhibitor 2A
CFR	Code of Federal Regulations (United States of America)
CI	Confidence interval
(CL_{CR})	Creatinine clearance
C_{max}	Maximum observed plasma drug concentration
CMO	Contract Manufacturing Organisation
CNS	Central nervous system
CRO	Contract research organisation
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DHFR	Dihydrofolate reductase

ABBREVIATION	Wording Definition
DL	Dose level
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DPD	Dihydropyrimidine dehydrogenase
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EoT	End of treatment
EPAR	European Public Assessment Report
EPCAM	Epithelial Cell Adhesion Molecule
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQol 5 dimension health status questionnaire (5 level)
ESMO	European Society for Medical Oncology
EU	European Union
FBE	Free base equivalent
FDA	Food and Drug Administration
FOLFIRINOX	Irinotecan+oxaliplatin+5-FU/LV
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GNAS	Guanine nucleotide-binding protein, alpha-stimulating activity polypeptide 1
HAART	Highly active antiretroviral therapy
HAS	Haute Autorité de Santé (French National Authority for Health)
HCG	Human chorionic gonadotrophin
Hgb	Haemoglobin
HIV	Human immunodeficiency virus
HR	Hazard Ratio
HSD	Hwang-Shi-Decani
i.v.	Intravenous

ABBREVIATION	Wording Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
INCa	Institut National du Cancer (French National Cancer Institute)
IRB	Institutional review board
ITT	Intention to treat
IWRS	Interactive Web Response System
KRAS	Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LC	Liquid chromatography
LV	Leucovorin
MDD	Medical Development Director
MedDRA	Medical Dictionary for Regulatory Activities
MLH1	Human MutL homolog 1
MRI	Magnetic resonance imaging
MSH2	Human MutS homolog 2
MSH6	MutS (E.coli) homolog 6
NCCN	National Comprehensive Cancer Network
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
PALB2	Partner and localizer of the BRCA2 gene
PBRM1	Polybromo 1 gene
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per protocol
PRO	Patient Reported Outcome
QLQ-C30	Quality-of-life core 30 questionnaire
QLQ-PAN26	Quality-of-life questionnaire pancreatic cancer module

ABBREVIATION	Wording Definition
QoL	Quality of life
QTcF	QT interval corrected by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RNF43	Ring Finger Protein 43 gene
RREB1	Ras Responsive Element Binding Protein 1
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System®
SCLC	Small cell lung cancer
SD	Standard deviation
SMAD4	Mothers against decapentaplegic homolog 4
SmPC	Summary of Product Characteristics
SN-38	Irinotecan active metabolite
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TGFbR2	Transforming Growth Factor Beta Receptor 2
t_{max}	Time to maximum observed drug concentration
TOP 1	Topoisomerase I
TP53	Tumour Protein p53
TTF	Time to treatment failure
TTR	Time to Response
UDP	Human uridine diphosphate
UGT	UDP-glucuronosyltransferase
UGT1A1	Uridine diphosphate glucuronosyl transferase 1A1
UGT1A1*28	UGT1A1 pharmacogenetic variant *28
ULN	Upper limit of normal
US(A)	United States (of America)
USPI	United States package insert
WBC	White blood cell(s)
WOCBP	Women of child-bearing potential

1 BACKGROUND INFORMATION

1.1 Introduction

Pancreatic adenocarcinoma and its variants account for over 90% of pancreatic malignancies and is one of the most difficult to treat cancers [NCCN 2020, Lambert 2019]. Compared with most other cancers, pancreatic cancer is associated with a poor prognosis; it is one of the tumours with the least favourable outlook in terms of survival: mortality from pancreatic cancer is almost identical to its incidence with a mortality to incidence ratio of 0.94 [Bray 2018]. Pancreatic cancer is often diagnosed late in the natural history of the disease due to lack of screening tests, symptoms being largely nonspecific and not usually appearing until the disease has progressed [Evans 2014, Saftoiu 2020, Henrikson 2019]. Owing to the lack of early symptoms and the aggressive nature of the disease, up to 80% of patients with pancreatic adenocarcinoma receive a diagnosis at an advanced stage, by which time the tumour is unresectable [Martinez-Bosch 2018, Lambert 2019].

Despite recent advances in the management of pancreatic adenocarcinoma, poor survival rates continue, with a median overall survival (OS) of less than 1 year and a 5-year survival rate of 0-11% depending upon the geographic location. However, for patients with metastatic disease who comprise the majority of patients with pancreatic adenocarcinoma at the time of diagnosis, the 5-year survival is only 3% [ACS 2020, Rawla 2019, Cancer statistics in Japan 2017, Lambert 2019].

The American Cancer Society (ACS) estimated about 56,770 new cases of pancreatic cancer and about 45,750 deaths from pancreatic cancer in the United States (US) in 2019. Although pancreatic cancer constitutes only 3% of all new cases of cancers in the US, it is the fourth leading cause of cancer deaths, estimated that in 2019 it was responsible for 7% and 8% of all cancer-related mortalities in men and women respectively [Siegel 2019]. Similar trends have been observed in the European Union (EU) - an estimated 90,700 deaths from pancreatic cancer have been predicted for 2019 making it the fourth leading cause of cancer deaths and being responsible for 6.7% of all cancer-related mortalities[Malvezzi 2019]. Projections of the number of deaths from cancer indicate that pancreatic cancer will become the second leading cause of cancer related mortality by the year 2030 [Rahib 2014].

1.1.1 Pancreatic Cancer Treatment

Gemcitabine monotherapy was the major first-line metastatic pancreatic cancer treatment proven to prolong OS over 5-fluorouracil (5-FU) [Burris 1997], leading to the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approvals in 1996. Various gemcitabine-based combination therapies were then assessed with the aim of improving survival.

Attempts to improve on gemcitabine single agent activity by combining it with other available chemotherapies have been largely unsuccessful [Borazanci 2014, Teague 2015, Ko 2015]. Two combination chemotherapy regimens have emerged as new standards of care for first-line treatment of metastatic pancreatic cancer:

- 5-FU/leucovorin (LV)+irinotecan+oxaliplatin (FOLFIRINOX) and
- nab-paclitaxel+gemcitabine

These demonstrate median OS of 11.1 months (PRODIGE study) and 8.5 months (MPACT), respectively, in separate phase III studies [Conroy 2011, von Hoff 2013].

Given the poor prognosis and the low median survival rates of less than one year for patients with metastatic disease, new treatment options are still needed. In addition, research into novel and predictive biomarkers is important to manage this disease [Ko 2015].

Irinotecan liposome injection has been studied in a randomised, phase III, international study (NAPOLI-1), in which the regimen of irinotecan liposome injection and 5-FU/LV significantly prolonged OS compared to 5-FU/LV treatment alone in metastatic pancreatic cancer patients who had progressed following gemcitabine-based therapy [Wang Gillam 2016].

Irinotecan liposome injection in combination with 5-FU/LV was approved by the FDA, the EMA and other regulatory agencies worldwide for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Irinotecan liposome injection is also being studied in an ongoing phase II study to assess the safety, tolerability and efficacy in combination with oxaliplatin and 5-FU/LV in subjects with unresectable, locally advanced and metastatic adenocarcinoma of the pancreas who have not previously received chemotherapy in the metastatic setting (preliminary results in the Investigator's Brochure (IB) and summarised in Section 1.3.2).

The goal of the present study is to assess the efficacy and safety of irinotecan liposome injection, in combination with other anticancer therapies (i.e. 5-FU/LV and oxaliplatin) in subjects not previously treated for metastatic pancreatic cancer, compared to a nab-paclitaxel+gemcitabine control. Descriptions of the anticancer therapies to be used in combination regimens in this study are briefly described below.

1.1.1.1 Description of 5-Fluorouracil and Leucovorin

5-Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of deoxyribonucleic acid (DNA). It also interferes with ribonucleic acid (RNA) synthesis and is used in the treatment of carcinoma of the colon, rectum, breast, stomach and pancreas.

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by LV. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., 5-FU and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthase.

1.1.1.2 Description of Oxaliplatin

Oxaliplatin is a platinum-based drug that acts as a DNA cross-linking agent to effectively inhibit DNA replication and transcription, resulting in cytotoxicity which is cell-cycle non-specific. Oxaliplatin is typically used in combination with infusional 5-FU/LV and is approved for use in advanced colorectal cancer (refer to reference information for oxaliplatin for more details).

1.1.1.3 Description of Gemcitabine

Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumour activity and is approved for treatment of ovarian cancer in combination with carboplatin, breast cancer in combination with paclitaxel, non-small cell lung cancer in combination with cisplatin, and for pancreatic cancer as a single-agent or in combination with nab-paclitaxel (refer to reference information for gemcitabine for more details).

Gemcitabine acts on cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary, which ultimately results in the initiation of apoptotic cell death.

1.1.1.4 Description of Nab-paclitaxel

Nab-paclitaxel (trade name Abraxane®) is an albumin-bound form of paclitaxel, a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. The inhibition of normal microtubule network interferes with essential interphase and cellular functions. It is approved for the treatment of metastatic breast cancer, non-small cell lung cancer in combination with carboplatin, and adenocarcinoma of the pancreas in combination with gemcitabine (refer to reference information for nab-paclitaxel for more details).

1.2 Irinotecan Liposome Injection

Irinotecan liposome injection (also known as Nal-IRI, BAX2398, PEP02, liposomal irinotecan and MM-398) is encapsulated in a nanoliposome drug delivery system. This is referred to as liposomal irinotecan in Europe and has tradename Onivyde® in the USA and Onivyde pegylate liposomal® in Europe. The active ingredient of the irinotecan liposome injection is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water-soluble analogue of the naturally-occurring alkaloid, camptothecin. Topoisomerase I inhibitors work to arrest uncontrolled cell growth by preventing the unwinding of DNA and therefore preventing replication. The pharmacology of irinotecan is complex, with extensive metabolic conversions involved in the activation, inactivation, and elimination of the drug [Garcia-Carbonero 2002, Vanhoefer 2001, Drummond 2006]. Irinotecan is a pro-drug that is converted by nonspecific carboxylesterases into a 100 to 1000-fold more active metabolite, SN-38 [Kang 2014]. SN-38 is cleared via glucuronidation, (for which major pharmacogenetic differences have been shown), and biliary excretion. These drug properties contribute to the marked differences in efficacy and toxicity observed in clinical studies with irinotecan [Kalra 2014, Tsai 2011].

Drug carrier technologies represent a rational strategy to improve the pharmacokinetics (PK) and biodistribution of irinotecan while protecting it from premature metabolism. Irinotecan liposome injection employs a novel intraliposomal drug stabilisation technology for encapsulation of irinotecan into long-circulating liposome-based nanoparticles with high drug load and high in vivo stability. The stable nanoliposome formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release should improve activity of this schedule-dependent drug by increasing duration of exposure of tumour tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the more sensitive S-phase of the cell cycle. The improved PK, high intravascular drug retention in the liposomes and enhanced permeability and retention effect may potentially result in site-specific drug delivery to solid tumours. Stromal targeting results from the subsequent depot effect, where liposomes accumulating in tumour associated macrophages release their payload, which is then converted locally to the substantially more cytotoxic SN-38. The preferentially local bioactivation should result in reduced exposure to potential sites of toxicity and increased exposure to neighbouring cancer cells within the tumour.

1.2.1 Irinotecan Liposome Injection Pre-Clinical Experience

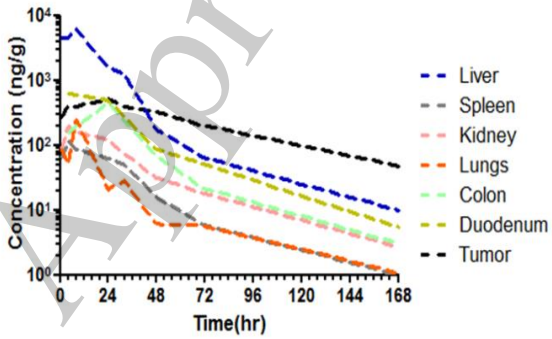
Irinotecan liposome injection has been shown in pre-clinical settings to have a broad spectrum of activity in a wide range of solid tumours including colon, pancreatic, gastric, cervical, non-small cell lung, small cell lung, ovarian, thyroid, and breast cancers, as well as glioma, Ewing's sarcoma, and neuroblastoma, often with a high degree of anti-tumour activity against resistant or difficult to treat cancer models [Drummond 2006, Kang 2014, Kalra 2014]. Irinotecan liposome injection has also shown potent antitumour activity, including durable tumour regressions, and was markedly superior to the equivalent dose of free drug in a bioluminescent-based orthotopic xenograft pancreatic model [Tsai 2011].

1.2.1.1 Irinotecan Liposome Injection Pre-Clinical Pharmacokinetics

The PK properties of irinotecan liposome injection were evaluated in an HT-29 colon cancer subcutaneous xenograft model, as reported by [Kalra 2014]. Both irinotecan and SN-38 were cleared very rapidly (within 8 hours) from the plasma following non-liposomal irinotecan administration; however, irinotecan liposome injection clearance was demonstrated to be considerably slower and remained in circulation for over 50 hours. SN-38 plasma exposure was also greater though maximum observed plasma drug concentration (C_{max}) levels were reduced following irinotecan liposome injection administration, suggesting the advantage of the irinotecan liposomal formulation in prolonging exposure and half-life via the ability of the lipid bilayer to protect the conversion of prodrug CPT-11 to SN-38. Further, both irinotecan and SN-38 accumulated in tissues for extended time (at least 1 week after administration of irinotecan liposome injection), yet there were relatively higher levels of prolonged accumulation in the tumour compared to normal tissue, where the metabolites are at very low levels after 48 hours (Figure 1).

Activation of irinotecan to SN-38 by the liver is the primary path for SN-38 tumoural accumulation when non-liposomal irinotecan is administered. In contrast, these data suggest that accumulation of irinotecan liposome injection in the tumour and subsequent liposome breakdown and local conversion of irinotecan to SN-38 is responsible for the enhanced tumour exposure to SN-38 when irinotecan liposome injection is administered. These preclinical data demonstrating longer retention time in tumour lesions with irinotecan liposome injection administration compared to non-liposomal irinotecan administration formed the basis for clinical development.

Figure 1 Tissue Distribution of Irinotecan Liposome Injection in an HT-29 Xenograft Study.



Levels of SN-38 in various tissues following a single irinotecan liposome injection (20 mg/kg) dose are shown. Prolonged accumulation of SN-38 (~168 h) seen in tumour compared to other organs (~48 h).

1.2.2 Irinotecan Liposome Injection Clinical Experience

Irinotecan liposome injection has been studied in subjects with solid tumours, including cervical cancer, gastric cancer, pancreatic cancer, and colorectal cancer. Disease areas currently being studied include glioma (intravenous (i.v.) and convection-enhanced local delivery), breast cancer and several paediatric solid tumours, including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, osteosarcoma and small cell lung cancer (SCLC). Clinical studies of irinotecan liposome injection have been completed to date, with over 600 subjects across multiple tumour types exposed to various dosing regimens, with other studies actively recruiting subjects across multiple tumour types (see IB).

1.2.2.1 Ongoing MM-398-07-02-03 Phase II Study

Study MM-398-07-02-03 (CCI , EudraCT Number: 2015-003086-28) is an ongoing open-label, phase II study to assess the safety, dose-limiting toxicities (Part 1A only), tolerability and efficacy of irinotecan liposome injection in combination with oxaliplatin and 5 FU/LV in subjects with unresectable, locally advanced and metastatic adenocarcinoma of the pancreas who have not previously received chemotherapy in the metastatic setting.

Study MM-398-07-02-03 comprises a complete initial dose exploration (Part 1A) followed by dose expansion (Part 1B: ongoing) of the irinotecan liposome injection+oxaliplatin+5-FU/LV regimen.

Subjects were enrolled in cohorts following a 3+3 dose escalation design in Part 1A, (n=31), to select the dose level of the combination of oxaliplatin and irinotecan liposome injection. Following four dose exploration cohorts (Part 1A), a recommended dose (irinotecan liposome injection 50 mg/m^2, oxaliplatin 60 mg/m^2, LV 400 mg/m^2, 5-FU 2400 mg/m^2 every 2 weeks - Cohort B) for expansion (Part 1B) was selected based on dose-limiting toxicities and cumulative safety. The expansion phase enrolled an additional 25 subjects at the selected dose level. A total of 56 patients have been enrolled and treated in Parts 1A and 1B.

An interim data analysis for safety and efficacy was performed with data cut-off 19 February 2019 after all subjects in the dose-expansion cohort had completed the second scheduled tumour evaluation at 16 weeks.

The pooled population (n=32) included all subjects treated at the recommended dose for expansion (irinotecan liposome injection 50 mg/m^2, oxaliplatin 60 mg/m^2, LV 400 mg/m^2, 5-FU 2400 mg/m^2 every 2 weeks - Cohort B of Part 1A n=7; Part 1B n=25). The best overall response in the pooled analysis was complete response (CR) in one subject (diagnosed with locally advanced Stage III disease), partial response (PR) in 10 subjects, and stable disease (SD) in 15 patients (sum of CR+PR+SD: 81.3%), with an overall response rate (ORR) of 34%. 23 of 32 patients (71.9%) achieved disease control at 16 weeks. At the time of data cut-off, 15 of 32 subjects in the pooled population analysis remained on treatment.

For the 56 subjects treated, all (100.0%) had TEAEs. There were nine TEAEs that were defined as dose limiting toxicities (DLTs) that were reported by five subjects across the four dose exploration cohorts (diarrhoea, n=2; vomiting, anal fissure, anal inflammation, proctalgia, neutropenic infection, neutropenic sepsis, and febrile neutropenia, all n=1), including one subject treated in Part 1A Cohort B who was included in the pooled analysis (febrile neutropenia).

Treatment-related TEAEs Grade 3 or higher were reported by 39 of 56 subjects, including 20 subjects from the pooled analysis of 32 subjects treated with irinotecan liposome injection 50 mg/m^2 + LV 400 mg/m^2 + 5-FU 2400 mg/m^2, and oxaliplatin 60 mg/m^2. The TEAEs included: neutropenia, n=9; febrile neutropenia, hypokalaemia, both n=4; diarrhoea, nausea, both n=3; anaemia, vomiting, both n=2, with no reported Grade 3 or higher fatigue or peripheral neuropathy.

SAEs were reported by 31 of the 56 treated subjects, including 14 of the 32 subjects in the pooled analysis, with 23 subjects reporting treatment-related SAEs. In the pooled analysis, 10 of the 32 subjects had treatment-related SAEs: nausea, febrile neutropenia, both n=3; diarrhoea, vomiting, both n=2; colitis, enterocolitis, stomatitis, anaemia, pneumonia, and pyrexia, all n=1. At the data cut-off there were no treatment-related TEAEs leading to death.

More data from this study are provided in the Investigator's Brochure.

1.2.2.2 Irinotecan Liposome Injection Safety in Humans

Preliminary safety results for Study MM-398-07-02-03, where subjects with pancreatic cancer were given first line treatment with irinotecan liposome injection in a combination regimen with 5-FU/LV and oxaliplatin are presented in Section 1.2.2.1 and also in the IB.

The NAPOLI-1 study was the pivotal study for obtaining marketing approval for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy with irinotecan liposome injection in a combination regimen with 5-FU/LV (i.e. no regimen in the NAPOLI-1 study included oxaliplatin). With respect to irinotecan liposome injection, when used in combination with 5-FU and LV, the most common adverse reactions (≥20 %) observed in clinical trials considered to be related to the regimen are: diarrhoea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anaemia, stomatitis and pyrexia. The overall safety profile of irinotecan liposome injection is presented in detail in the IB. Table 2 summarises ≥ Grade 3 safety data from the NAPOLI-1 trial comparing irinotecan liposome injection+5-FU/LV (at a dose of 70 mg/m^2 (FBE) given on an every 2 week schedule), or irinotecan liposome injection monotherapy (at a dose of 100 mg/m^2 (FBE) given on an every 3 week schedule), with 5-FU/LV alone (given weekly for 4 weeks followed by 2 weeks of rest) in the same population of subjects who had received prior gemcitabine therapy.

Table 2 Summary of Grade 3 or Higher Adverse Events in NAPOLI-1 Study

	Irinotecan liposome injection + 5-FU/LV[a] (N=117)	Irinotecan liposome injection[b] (N=147)	5-FU/LV[c] (N=134)
Grade ≥3 non-haematologic AEs in >5% subjects, %			
Fatigue	14	6	4
Diarrhoea	13	21	5
Vomiting	11	14	3
Nausea	8	5	3
Asthenia	8	7	7
Abdominal pain	7	8	6
Decreased appetite	4	9	2
Hypokalemia	3	12	2
Hypernatremia	3	6	2
Grade ≥3 haematologic AEs based on laboratory values, % [d, e]			
Neutrophil count decreased	20	16	2
Haemoglobin decreased	6	7	5
Platelet count decreased	2	1	0

AE=adverse event, FBE=free base equivalent, 5-FU=5-fluorouracil, LV=leucovorin
Data from phase III NAPOLI study of nal-IRI+5-FU/LV vs. 5-FU/LV [Wang-Gillam 2016]
a Irinotecan liposome injection at 70 mg/m^2 FBE, oxaliplatin followed by LV 400 mg/m^2 over 30 min, then 5-FU 2400 mg/m^2 over 46 h, every 2 weeks.
b Irinotecan liposome injection 100 mg/m^2 FBE every 3 weeks.
c LV 200 mg/m^2 as a 30-min infusion followed by an infusion of 5-FU 2000 mg/m^2 over 24 h, every week for the first 4 weeks of each 6-week cycle.
d Per CTCAE Version 4
e Includes only subjects who had at least one post-baseline assessment

It has been shown in animal and human PK studies that once irinotecan is released from the irinotecan liposome injection liposomes, the conversion of irinotecan to SN-38 is similar to that of the unencapsulated irinotecan. The safety of irinotecan liposome injection, therefore, may be indirectly compared with the safety of non-liposomal irinotecan, primarily based on a qualitative comparison of adverse reactions, as reported in the Camptosar® United States package insert (USPI) for irinotecan [Camptosar® USPI 2016]. The comparison is qualitative, as both irinotecan and irinotecan liposome injection have been used in different doses and

schedules as monotherapy and combination therapy with other chemotherapeutic agents; therefore, quantitative comparisons are difficult. The most common adverse reactions of irinotecan and irinotecan liposome injection are similar and are mainly gastrointestinal events and myelosuppression.

The common adverse reactions (>30%) observed in clinical studies with irinotecan in combination with other agents are: nausea, vomiting, abdominal pain, diarrhoea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anaemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia. The common adverse reactions (>30%) observed in single agent irinotecan therapy in clinical studies are: nausea, vomiting, abdominal pain, diarrhoea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anaemia, asthenia, fever, body weight decreasing, and alopecia see Camptosar® USPI [Camptosar® USPI 2016].

1.2.2.3 Irinotecan Liposome Injection Clinical Efficacy in Pancreatic Cancer

Clinical efficacy of irinotecan liposome injection has been demonstrated in gemcitabine-refractory metastatic pancreatic cancer subjects: in a randomised, phase III, international study (NAPOLI-1), in which irinotecan liposome injection was given as a monotherapy, or in combination with 5-FU/LV, compared to the control arm of 5-FU/LV alone [Wang-Gillam 2016]. The majority of subjects enrolled in this study had received prior chemotherapy in the metastatic setting (others received gemcitabine as neoadjuvant or adjuvant therapy). Approximately one half of subjects were categorised as second-line, and approximately a third of subjects were post-second line in the metastatic setting. The irinotecan liposome injection+5-FU/LV combination significantly prolonged OS compared to 5-FU/LV treatment alone. The median OS for the irinotecan liposome injection+5-FU/LV regimen arm was 6.1 months compared to 4.2 months for the 5-FU/LV alone control arm with an unstratified hazard ratio (HR) of 0.67 (95% confidence interval (CI): 0.49 to 0.92, p=0.012). The irinotecan liposome injection monotherapy arm demonstrated a median OS of 4.9 months (compared to 4.2 months in the control arm); although this was not a statistically significant difference, there was numerical improvement in overall response rate (ORR) and CA19-9 response, suggesting activity of irinotecan liposome injection alone. Further, in subjects who received ≥80% of the protocol defined treatment during the first 6 weeks of treatment (the per protocol (PP) analysis), the irinotecan liposome injection+5-FU/LV regimen arm achieved a median OS of 8.9 months versus 5.1 months for the control arm (HR 0.57, 95% CI: 0.36 to 0.88, p=0.0117). The ORR in the irinotecan liposome injection+5-FU/LV regimen arm was 16% versus 1% on the control arm (p<0.001) [Chen 2015]. The results from this study are very promising and provide motivation for testing irinotecan liposome injection in pancreatic cancer patients not previously treated with gemcitabine.

A more detailed description of the product is provided in Section 6.1.

1.3 Known and Potential Risks and Benefits to Human Subjects

1.3.1 Risks

1.3.1.1 Lack of Efficacy

While there is a potential risk of lack of efficacy of irinotecan liposome injection, as this irinotecan formulation has not been studied in a phase III study in subjects with untreated metastatic pancreatic adenocarcinoma, it is considered to be low. Activity of non-liposomal irinotecan in this setting has been observed in the FOLFIRINOX clinical study [Conroy 2011] and irinotecan liposome injection has demonstrated activity in this disease supported by the NAPOLI-1 trial [von Hoff 2014].

1.3.1.2 Safety Risks

Irinotecan liposome injection in combination with 5-FU/LV has been approved in 39 countries since 2015 for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. The safety profile has been described in the IB and in labelling (e.g. the USPI).

The results for 56 subjects treated in the ongoing phase II Study MM-398-07-02-03 with the regimen irinotecan liposome injection+oxaliplatin+ 5-FU/LV can be found in the IB and are summarised in Section 1.2.2.1. As seen from these results, the overall safety risks for the combination regimen irinotecan liposome injection+oxaliplatin+5-FU/LV are similar to those observed in the PRODIGE phase III study in pancreatic cancer [Von Hoff 2013], which include neutropenia, hypokalaemia, diarrhoea, nausea, anaemia and vomiting. No new safety signals were observed when compared to the Onivyde® USPI [Onivyde® USPI 2017].

Caution should be exercised when using irinotecan liposome injection in subjects with body mass index <18.5 kg/m^2.

Specific safety risks for 5-FU, LV and oxaliplatin, separately, in Arm 1 and nab-paclitaxel and gemcitabine in Arm 2, are described below.

Potential Toxicities with 5-Fluorouracil (Arm 1 only)

Stomatitis and esophago-pharyngitis (which may lead to sloughing and ulceration), diarrhoea, anorexia, nausea, emesis and myelosuppression are commonly seen with treatment; alopecia and dermatitis, in the form of pruritic rash usually appearing on the extremities, may also be seen (see the reference information for 5-FU). Very common adverse events (AEs) (≥20%) that were observed with irinotecan liposome injection in combination with 5-FU/LV in clinical trials considered to be related were: diarrhoea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anaemia, stomatitis and pyrexia.

Part of the toxicities following treatment with 5-FU may be related to deficiency in the activity of the main enzyme enabling elimination of 5-FU, dihydropyrimidine dehydrogenase (DPD). This deficiency can be low (around 3 to 8% of individuals) or absent (between 0.01 and 0.5% of individuals).

In March 2020, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that patients should be tested for deficiency of DPD before starting cancer treatment with 5-FU. PRAC recommends that patients with a known complete DPD deficiency must not be given 5-FU intravenously as a complete lack of working DPD puts them at higher risk of severe and life-threatening side effects. In addition, for patients with a partial DPD deficiency, PRAC recommends a reduced starting dose of 5-FU; since the effectiveness of a reduced dose has not been established, following doses may be increased if there are no serious side effects [PRAC Guidelines 2020].

Given the heterogeneity in clinical practice and lack of consensus clinical guidelines for starting dose modifications, subjects with known low or absent DPD activity will be excluded from this study.

Potential Toxicities with Oxaliplatin (Arm 1 only)

The following AEs are relatively common (≥40%) with oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the irinotecan liposome injection containing regimen: peripheral sensory neuropathy, neutropenia, thrombocytopenia, anaemia, nausea, increases in transaminases and alkaline phosphatase, diarrhoea, fatigue, emesis, and stomatitis. In a phase III study of the FOLFIRINOX regimen (5-FU/LV+irinotecan+oxaliplatin), the most common (>5%) Grade 3 or 4 AEs were: neutropenia, fatigue, vomiting, diarrhoea, thrombocytopenia, sensory neuropathy, anaemia, elevated alanine aminotransferase (ALT) level, thromboembolism, and febrile neutropenia [Conroy 2011]. Grade 3 or 4 hypersensitivity

reactions, including anaphylactic reactions, have been observed in 2 to 3% of colon cancer patients receiving oxaliplatin. See Section 6.2.4 for guidelines on the management of infusion reactions. Additional AEs such as nausea, fever and injection site reaction, may be anticipated, as described in the reference information for oxaliplatin. There needs to be caution if oxaliplatin is co-administered with other medicinal products known to cause QT interval prolongation or rhabdomyolysis.

Potential Toxicities with Nab-paclitaxel and Gemcitabine (Arm 2 only)

The most common adverse reactions (≥20%) for single agent gemcitabine are nausea/vomiting, anaemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral oedema.

The following AEs are relatively common (≥20%) with nab-paclitaxel and gemcitabine combination treatment: neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral oedema, diarrhoea, pyrexia, vomiting, decreased appetite, rash, and dehydration.

Severe hypersensitivity reactions with fatal outcome have been reported with nab-paclitaxel treatment; see Section 6.2.4 for guidelines on the management of infusion reactions. Additional AEs may be anticipated, as described in the reference information for nab-paclitaxel and gemcitabine.

Other Toxicities Requiring Special Attention

For both treatment arms, QTc prolongation that occurs in the setting of diarrhoea induced electrolyte imbalance should be treated with appropriate electrolyte repletion. Once the underlying abnormality is corrected and the electrocardiogram (ECG) abnormalities have reversed, treatment may continue under careful monitoring and with appropriate dose modification for diarrhoea as described in Section 6.3.3.2.

Care of Intravenous Site:

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile saline and applications of ice are recommended, or as per institutional standard of care.

NAPOLI-1 Study Risk Assessment

Safety results from the NAPOLI-1 study, which was the pivotal study for obtaining marketing approval for second line treatment of pancreatic cancer with irinotecan liposome injection in a combination regimen with 5-FU/LV, are summarised in Section 1.2.2.2 and the IB.

Irinotecan hydrochloride trihydrate is a known active substance, with a well-established safety profile. In the NAPOLI-1 study, most of the treatment-emergent adverse events (TEAEs) in combination with 5-FU/LV were manageable with supportive therapy, dose delays or both [Onivyde European Public Assessment Report (EPAR)]. The following adverse reactions, considered to be possibly or probably related to the administration of irinotecan liposome injection, were reported in 264 subjects with metastatic adenocarcinoma of the pancreas and listed in the EU Summary of Product Characteristics (SmPC), 147 of whom received irinotecan liposome injection in monotherapy (100 mg/m^2 FBE) and 117 subjects received irinotecan liposome injection (70 mg/m^2 FBE) in combination with 5-FU/LV. The most common adverse reactions (incidence ≥20%) with combination treatment were: diarrhoea, nausea, vomiting, decreased appetite, neutropenia, fatigue, asthenia, anaemia, stomatitis and pyrexia. The most common serious adverse reactions (≥2%) of irinotecan liposome injection therapy were diarrhoea, vomiting, febrile neutropenia, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia. The EPAR states that 'no unexpected safety findings emerged so far from the liposomal irinotecan development program to challenge what is previously known from standard irinotecan'.

The EU Risk Management Plan lists potential risks (embryotoxicity or teratogenicity, hypersensitivity reactions, medication errors related to drug/dose confusion with non-liposomal irinotecan and interstitial lung disease) as well as missing information (use in patients with hepatic impairment and patients with renal impairment) [Onivyde EPAR 2016]. Subjects with metastatic adenocarcinoma of the pancreas, who will receive irinotecan liposome injection in this study might be exposed to the same potential safety risks. These are listed in the irinotecan liposome injection IB and considered or mitigated in the different sections of the study protocol, e.g. exclusion criteria (Section 4.2), description of study medications including investigational medicinal products (IMPs) (Section 6.2) and use of concomitant therapies (Section 6.3).

1.3.2 Benefits

Based on current clinical experience, it is considered that irinotecan liposome injection+oxaliplatin+5-FU/LV represents a novel therapeutic approach for first-line treatment of patients with metastatic pancreatic cancer, which is currently a high unmet clinical need. By adding oxaliplatin to irinotecan liposome injection and 5-FU/LV the potential to increase DNA damage and potentiate efficacy exists. In addition, due to the prolonged PK properties of irinotecan liposome injection and sustained tumour exposure, it is thought that using irinotecan liposome injection instead of conventional irinotecan would improve upon the efficacy and tolerability of the standard FOLFIRINOX regimen. Building on prior experience from the standard FOLFIRINOX regimen, the objective is to demonstrate a 3-month improvement in OS versus the approved regimen of gemcitabine+nab-paclitaxel.

The IB gives efficacy (and safety) results from the ongoing phase II Study MM-398-07-02-03, during which subjects received first-line treatment for metastatic pancreatic cancer with irinotecan liposome injection+oxaliplatin+5-FU/LV. Overall 56 subjects were enrolled and treated, and as of data cut off 32 subjects had been treated (in both parts of the study) at the selected dose level (see Section 1.2.2.1).The best overall response (BOR) in the pooled analysis for 32 subjects treated with irinotecan liposome injection 50 mg/m^2 + oxaliplatin 60 mg/m^2+ 5-FU/LV 2400/400 mg/m^2 was: complete response in one subject (diagnosed with locally advanced Stage III disease), partial response in 10 subjects, and stable disease in 15 subjects (sum of complete response +partial response +stable disease: 81.3%), with an ORR of 34%.

1.4 Selection of Investigational Medicinal Products and Dosages

The rationale for the proposed combination regimen is based on the clinical results of Study MM-398-07-02-03. This study included an initial dose exploration (Part 1A) followed by dose expansion (Part 1B) of the irinotecan liposome injection+oxaliplatin+5-FU/LV regimen as detailed in Section 1.2.2.1. This preliminary safety analysis provides reassurance that the safety profile of each of the drugs is in line with the expected safety profile of each of the drugs within the regimen and can be administered to subjects with pancreatic cancer.

The proposed study design regimen for Arm 1 includes irinotecan liposome injection at a dose of 50 mg/m^2 (FBE), the recommended starting dose for subjects homozygous for the UGT1A1*28 allele; hence, there is no reason to suggest a different starting dose for subjects homozygous for the UGT1A1*28 allele. As part of this study, pharmacogenomic data will be collected on all subjects for determination of UGT1A1*28 status at baseline. As per the scheduled assessments, all subjects will be monitored closely for haematological toxicities, with specific guidance for full blood count thresholds prior to dosing and dose modifications for haematological toxicities, which will also be monitored and evaluated by the Independent Data Monitoring Committee (IDMC) (see Section 11.6 for information about the IDMC).

Nab-paclitaxel (tradename: Abraxane®) in combination with gemcitabine has been chosen as the control arm based on its approval in the US, in the EU and in other territories for first-line treatment of patients with metastatic adenocarcinoma of the pancreas, its robust OS benefit

demonstrated in the same patient population intended to be enrolled in the study (ECOG performance status 0 or 1, which is similar to Karnofsky Performance Status ≥70, [Oken 1982]), on its inclusion in clinical practice guidelines and on its widespread clinical use in this disease setting.

- An OS benefit was demonstrated in this patient population in the registration study for nab-paclitaxel (the MPACT study). The median OS was 8.5 months in the gemcitabine+nab-paclitaxel arm compared with 6.7 months in the gemcitabine arm (HR 0.72, 95% CI: 0.62 to 0.83, p<0.001). [von Hoff 2013]
- The administration of nab-paclitaxel in combination with gemcitabine is recommended by the National Comprehensive Cancer Network (NCCN) [NCCN Guidelines Pancreatic Adenocarcinoma, Version 1.0 2020] and European Society for Medical Oncology (ESMO) Clinical Practice Guidelines [Ducreux 2015 with 2019 update] as a category 1 (preferred) option for patients with metastatic adenocarcinoma of the pancreas
- There is widespread clinical use of nab-paclitaxel in combination with gemcitabine in this disease setting. [Abrams 2017].

Further details on administration procedures and dosage are provided in Section 6.2.

1.5 Population to be Studied

The study will enrol adult subjects with metastatic adenocarcinoma of the pancreas who have not previously received chemotherapy. Because subjects will be randomised to either of the two arms, the inclusion and exclusion criteria (Sections 4.1 and 4.2) reflect contraindications and restrictions for both regimens.

Similar to the population included in the MPACT study of first-line treatment of subjects with metastatic adenocarcinoma of the pancreas, subjects will be enrolled with ECOG performance status 0 or 1 (similar to Karnofsky performance status ≥70 [von Hoff 2013]). Table 3 summarises the Karnofsky performance status of subjects at baseline in the MPACT study.

Table 3 Summary of Subject Karnofsky Performance Score at Baseline (MPACT Study)

Karnofsky Performance Status	Nab-paclitaxel+gemcitabine (N=431) n/N (%)	Gemcitabine alone (N=430) n/N (%)	Total (N=861) n/N (%)
100	69/429 (16)	69/429 (16)	138/858 (16)
90	179/429 (42)	199/429 (46)	378/858 (44)
80	149/429 (35)	128/429 (30)	277/858 (32)
70	30/429 (7)	33/429 (8)	63/858 (7)
60	2/429 (<1)	0/429	2/858 (<1)

Data Source: [von Hoff 2013] Table 1

1.6 Compliance Statement

The study will adhere to all local regulatory requirements and relevant company policies. The sponsor will ensure that the countries where the data are transferred provide an adequate level of protection to the data.

The study will be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented.

In case of data transfer outside the EU, the sponsor will either ensure that the countries where the data are transferred provide an adequate level of data protection or that the company receiving the data has joined the EU-US Privacy Shield Framework or will put in place a

contract including standard contractual clauses adopted by the European Commission to ensure that the transfer of study information complies with applicable data protection legislation. Such a contract can be made available upon request.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

This study is designed to evaluate the efficacy of the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV versus nab-paclitaxel+gemcitabine in improving OS in subjects with metastatic adenocarcinoma of the pancreas who have not previously received chemotherapy.

Nab-paclitaxel+gemcitabine has been selected as the comparator arm treatment, as it is FDA and EMA approved and widely used regimen for first-line treatment of a well characterised and identifiable population of adult patients with metastatic adenocarcinoma of the pancreas.

2.1.1 Study Rationale

Given the limited options for patients, the overall poor prognosis and the low median survival rates of less than one year for patients with metastatic disease, development of new treatments is still a necessity. In addition, research into novel and predictive biomarkers is important to manage this disease [Ko 2015, Garrido-Laguna 2015].

2.1.1.1 Unmet Clinical Need

Pancreatic cancer is associated with an extremely poor prognosis for several reasons. It is usually diagnosed at an advanced stage, which is often due to presentation with non-specific or no symptoms, a lack of sensitive and specific biomarkers, and difficulties in imaging early stage disease. Pancreatic cancer is also very aggressive, with perineural and vascular early growth and early distant metastases which preclude curative surgery in most cases. It is also characterised by a remarkable resistance to most conventional treatment options, including chemotherapy, radiotherapy and molecularly targeted therapy. Finally, pancreatic cancer harbours multiple genetic and epigenetic alterations and have dense tumour microenvironments shown to impede drug delivery. Despite some incremental progress in areas of research and patient care, the overall effect on the prognosis of patients with advanced pancreatic cancer has been marginal and these factors result in low observed OS rates. Thus, the development of improved systemic treatments remains a top priority for pancreatic cancer.

During the last two decades since gemcitabine approval, two gemcitabine combination regimens emerged as FDA approved therapies for first-line treatment of metastatic pancreatic cancer: nab-paclitaxel+gemcitabine, and erlotinib+gemcitabine. Erlotinib+gemcitabine was not chosen for the control arm due to modest improvements in the OS and limited clinical use in the disease setting. The median OS in the gemcitabine+erlotinib arm was 6.4 months compared with 6.0 months in the gemcitabine+placebo arm (HR 0.81, 95% CI: 0.68 to 0.97, p=0.028). [Erlotinib 2010].

Since the approval of gemcitabine in 1997, no phase III trial in advanced/metastatic disease had demonstrated a clinically and statistically significant improvement in OS over gemcitabine monotherapy until recently. The treatment landscape for metastatic disease has evolved to include two key regimens: irinotecan, oxaliplatin and 5-FU/LV (FOLFIRINOX) and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine. [von Hoff 2013, Conroy 2011] The nab-paclitaxel plus gemcitabine regimen is the only FDA and EMA approved regimen for this patient population. Currently, the NCCN [NCCN Clinical Guidelines Pancreatic Adenocarcinoma, Version 1.0 2020] and ESMO [Ducreux 2015 with 2019 update] recommend treatment with FOLFIRINOX or nab-paclitaxel+gemcitabine as standards of care for patients with metastatic pancreatic cancer. Age, performance status and other clinical factors are considered when deciding which regimen is appropriate. Gemcitabine monotherapy is currently reserved for patients who are not eligible to receive combination chemotherapy.

2.1.1.2 Targeting a Validated Target: Topoisomerase I

Irinotecan is an antineoplastic agent of the topoisomerase I (TOP 1) inhibitor class. DNA topoisomerases are a class of enzymes involved in the regulation of DNA supercoiling. Type I topoisomerases change the degree of supercoiling of DNA by causing single-strand breaks and relegation. Inhibition of TOP I stabilises the complex between TOP I and DNA which collides with moving DNA replication forks, eventually leading to double stranded DNA damage and ultimately cell death. It is a well-established fact that increased cytotoxicity of TOP I inhibitors is associated with sustained exposure.

TOP I is a validated drug target in metastatic adenocarcinoma of the pancreas. Irinotecan and irinotecan liposome injections are both referred to in guidelines for the treatment of metastatic adenocarcinoma of the pancreas as per the FOLFIRINOX regimen mentioned above for irinotecan and as part of a combination with 5-FU/LV for irinotecan liposome injection. Irinotecan and its active metabolite SN-38 bind to the TOP I - DNA complex and prevent relegation of the single-strand breaks. Liposomal delivery of irinotecan provides a mechanism for sustained inhibition of TOP I and prolong the duration of active therapy at the site of tumour cells to inhibit tumour growth.

2.1.1.3 Clinical Data Generated in Metastatic Pancreatic Adenocarcinoma with Irinotecan Liposome Injection

Clinical efficacy of irinotecan liposome injection has been demonstrated in gemcitabine-refractory metastatic pancreatic cancer patients: in a randomised, phase III, international study (NAPOLI-1), irinotecan liposome injection was given as a monotherapy, or in combination with 5-FU/LV, compared to the control arm of 5-FU/LV alone [Wang-Gillam 2016]. The majority of subjects enrolled in this study had received prior chemotherapy in the metastatic setting (others received gemcitabine as neoadjuvant or adjuvant therapy). Approximately half of subjects were categorised as second-line, and approximately one third of subjects were post-second line in the metastatic setting. The irinotecan liposome injection+5-FU/LV regimen significantly prolonged OS compared to 5-FU/LV treatment alone. The median OS for the irinotecan liposome injection+5-FU/LV regimen arm was 6.1 months compared to 4.2 months for the 5-FU/LV alone control arm with an unstratified HR of 0.67 (95% CI: 0.49 to 0.92, p=0.012). The irinotecan liposome injection monotherapy arm demonstrated a median OS of 4.9 months (compared to 4.2 months in the control arm); although this was not a statistically significant difference, there was numerical improvement in ORR and CA19-9 response, suggesting activity of irinotecan liposome injection alone. Further, in subjects who received ≥80% of the protocol defined treatment during the first 6 weeks of treatment (the per protocol analysis), the irinotecan liposome injection+5-FU/LV regimen arm achieved a median OS of 8.9 months versus 5.1 months for the control arm (HR 0.57, 95% CI: 0.36 to 0.88, p=0.0117). The ORR in the irinotecan liposome injection+5-FU/LV regimen arm was 16% versus 1% on the control arm (p <0.001). The results from this study were very promising and provide motivation for testing irinotecan liposome injection in pancreatic cancer patients not previously treated with gemcitabine.

2.1.1.4 Irinotecan+5-FU/LV+Oxaliplatin (FOLFIRINOX)

The regimen of 5-FU/LV+irinotecan+oxaliplatin (the FOLFIRINOX regimen) has been studied in multiple clinical trials. As mentioned previously, FOLFIRINOX has become a standard of care regimen for patients with good performance status based on the results of a single phase III trial conducted in France with 342 subjects showing median OS of 11.1 months versus 6.8 months for the gemcitabine alone control arm (HR 0.57, 95% CI: 0.45 to 0.73, p<0.001) [Conroy 2011]. The FOLFIRINOX regimen has been recommended by the NCCN and ESMO as a preferred option for first-line metastatic disease since 2011 [NCCN 2020, Ducreux 2015 with 2019 update].

In the current study, a modified FOLFIRINOX regimen will evaluate irinotecan liposome injection instead of conventional irinotecan, in order to improve the safety, tolerability and ultimately efficacy of the original FOLFIRINOX regimen. With irinotecan liposome injection dosing, the C_{max} of SN-38 is predicted to be lower than would be expected for standard dosing with non-liposomal irinotecan. Additionally, in a small phase II study in colorectal cancer, data suggest that irinotecan liposome injection+5-FU/LV may have less toxicity than non-liposomal irinotecan+5-FU/LV (the FOLFIRI regimen) [Chibaudel 2016]. Therefore, toxicity of the irinotecan liposome injection-containing triplet regimen is not expected to be greater than that seen with FOLFIRINOX.

In humans, the standard dose regimen of FOLFIRINOX which demonstrated efficacy is 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan (non-liposomal), LV infusion 400 mg/m^2 followed by 5-FU at a dose of 400 mg/m^2 administered by i.v. bolus followed by a continuous infusion of 2400 mg/m^2 [Conroy 2011]. Yet due to toxicity, modified FOLFIRINOX regimens are often used (e.g. elimination of the 5-FU bolus) with unknown effects on the efficacy and safety of modified schedules [Ducreux 2015]. In the current study, a modified triplet regimen is proposed, whereby no bolus of 5-FU will be administered. The doses of oxaliplatin and irinotecan liposome injection determined from the phase II combination regimens will be combined with the standard continuous infusion dose of 5-FU (excluding the bolus)/LV.

In the current study, the nab-paclitaxel+gemcitabine regimen will be compared to a regimen containing irinotecan liposome injection+oxaliplatin+5-FU/LV. While many gemcitabine-based combination regimens have been tested in clinical trials, nab-paclitaxel plus gemcitabine is the only approved standard of care regimen that offers significant benefit for first-line treatment of metastatic pancreatic cancer. The nab-paclitaxel+gemcitabine regimen is a preferred first-line treatment option according to the NCCN recommendations and ESMO Clinical Practice Guidelines [NCCN 2020, Ducreux 2015 with 2019 update]. In a phase III, international study of 861 subjects (MPACT trial), nab-paclitaxel+gemcitabine demonstrated a median OS of 8.5 months versus 6.7 months for gemcitabine alone (HR 0.72, 95% CI: 0.62 to 0.83, p; <0.001) [von Hoff 2013]. While nab-paclitaxel+gemcitabine is generally thought to be more tolerable than FOLFIRINOX, this regimen is associated with neuropathy and neutropenia, and has not been compared directly with FOLFIRINOX (Table 4) including the modified triplet regimen which substitutes irinotecan liposome injection instead of irinotecan.

Table 4 Summary of Comparisons between Clinical Studies

Regimens	Nal-IRI+5-FU-LV[a]	FOLFIRINOX[b]	Nab-paclitaxel+gemcitabine[c]
Setting	Post-gemcitabine	Front-line Metastatic Disease	
Efficacy			
Hazard Ratio	0.67	0.57	0.72
Median OS	6.1 months	11.1 months	8.5 months
Change versus Control	1.9 months	4.3 months	1.8 months
Adverse Events ≥ Grade 3			
Neutropenia	20%	45%	38%
Febrile neutropenia	2%	5%	3%
Fatigue	14%	24%	17%
Vomiting	11%	15%	<5%
Diarrhoea	13%	13%	6%
Neuropathy	None	9%	17%

5-FU=5-fluorouracil, LV=leucovorin, Nal-IRI=irinotecan liposome injection, OS=overall survival
a Data from phase III NAPOLI study of nal-IRI+5-FU/LV vs. 5-FU/LV [Wang-Gillam 2016]
b Data from phase III PRODIGE study of FOLFIRINOX vs. gemcitabine [Conroy 2011]
c Data from phase III MPACT study of nab-paclitaxel+gemcitabine vs. gemcitabine [von Hoff 2013]

2.1.1.5 Clinical Data for the CA19-9 Biomarker

Carbohydrate antigen 19.9 (CA19-9), is a prognostic tumour marker used to detect and monitor adenocarcinoma of the pancreas [Reni 2009, Chan 2014].

During the MPACT study, A total of 379 subjects in the nab-paclitaxel+gemcitabine group and 371 subjects in the gemcitabine group had a baseline CA19-9 measurement [von Hoff 2013]. A total of 61% of the subjects in the nab-paclitaxel+gemcitabine group, as compared with 44% of those in the gemcitabine group, had a decrease from baseline of at least 20% ($p<0.001$), and 31% versus 14% had a decrease of at least 90% ($p<0.001$). Subjects in the two treatment groups who had a decrease of at least 90% in the CA19-9 level had a median survival of 13.5 months, as compared with 8.2 months among those with a decrease of less than 90% (HR for death, 0.53; 95% CI, 0.43 to 0.67; $p<0.001$). A higher percentage of subjects in the nab-paclitaxel+gemcitabine group than in the gemcitabine group had a reduction of at least 90% in the CA19-9 level.

During the NAPOLI-I study, serial imaging studies and assessment of CA19-9 were undertaken at baseline and every 6 weeks until either disease progression, a new antineoplastic treatment was started, or withdrawal of consent [Wang-Gillam 2016]. There were 28 (29%) of 97 subjects allocated nanoliposomal irinotecan plus 5-FU/LV who achieved a CA19-9 response (≥50% decrease from abnormal baseline) versus seven (9%) of 81 assigned 5-FU/LV ($p=0.0006$).

*2.1.1.6 Clinical Data in UGT1A1*28 Homozygous Patients*

Human uridine diphosphate (UDP) glucuronosyltransferase (UGT) 1A1 is the enzyme that detoxifies neurotoxic bilirubin by conjugating it with glucuronic acid. Human UGT1A1 plays a critical role in the detoxification and excretion of endogenous and exogenous lipophilic compounds mainly in the liver and gastrointestinal tract. UGT1A1 is responsible for the glucuronidation of SN-38 to SN-38G as part of the mechanism of SN-38 clearance. Variation in TA-repeat length of a critical TATA box in the UGT1A1 promoter significantly contributes to enzyme activity with longer TA-repeat lengths showing lower expression than the wild-type. UGT1A1*28 (TA7) 7/7 homozygosity results in reduced UGT enzymatic activity and may result in elevated SN-38 levels and thereby contribute to increased SN-38 mediated toxicity following treatment with non-liposomal irinotecan.

Multiple studies have evaluated the association between UGT1A1*28 7/7 homozygosity, SN-38 concentration and safety in patients treated with non-liposomal irinotecan and suggest

the associations are dose-dependent. Much higher SN-38 concentrations were observed for UGT1A1*28 6/7 and 7/7 (compared to 6/6) when irinotecan was administered at a high dose of 300 mg/m^2 than when it was administered at a low dose of 15 to 75 mg/m^2 daily for 5 days for 2 consecutive weeks (41 to 159% versus 10 to 40%, respectively) [Iyer 2002, Stewart 2007]. In a study of 66 subjects who received single-agent non-liposomal irinotecan (350 mg/m^2 every 3 weeks), the incidence of Grade 4 neutropenia in subjects heterozygous (UGT1A1*28 6/7) and homozygous (7/7) for the UGT1A1*28 was 12.5% and up to 50% respectively [Camptosar® USPI 2016]. In a subsequent study, association between UGT1A1*28 homozygosity and haematological toxicity was observed only in subjects treated with >150 mg/m^2 non-liposomal irinotecan. By contrast, at lower dose of non-liposomal irinotecan (100 to 125 mg/m^2 every week) similar haematological toxicities were observed for both homozygous and non-homozygous subjects [Hoskins 2007]. However, more recent publications from prospective trials studying the FOLFIRI regimen (irinotecan dose of 180 mg/m^2) and the role of UGT1A1*28 polymorphism in toxicity and efficacy further suggest that the data are insufficient for recommending different dose adjustments in UGT1A1*28 homozygous patients [Toffoli 2006].

In patients treated with irinotecan liposome injection, the association between UGT1A1*28 homozygosity, SN-38, and haematologic toxicity is primarily obtained from study NAPOLI-1, where UGT1A1*28 homozygous subjects were treated at reduced dose (50 versus 70 mg/m^2 (FBE) every 2 weeks in combination with 5-FU/LV, or 70 versus 100 mg/m^2 (FBE) every 3 weeks monotherapy). The NAPOLI-1 study Population PK results are described in the IB and together with safety data confirms that the predicted Grade 3 or higher neutropenia was also similar if treated at 70 mg/m^2 (FBE) monotherapy (8.7% versus. 7.4%, respectively), or if treated at 100 mg/m^2 (FBE) monotherapy (15% versus 13%, respectively). An additional Population PK study presented in the IB showed that overall exposure to SN-38 was deemed similar between Japanese and non-Japanese populations with unrecognisable influence of UGT1A genotypes. Additionally, in a phase I study (UCSF 8103), no differences in toxicity were seen in cohorts of UGT1A1*28 6/7 (n=18) or 6/6 (n=16) subjects, and similar rates of dose limiting toxicities were seen in both cohorts. Based on these data, patients homozygous for UGT1A1*28, administered with the same dose of irinotecan liposome injection administration as non-homozygous patients, do not appear to be at significant clinical risk of increased Grade 3 or higher neutropenia.

Mechanistically, these data indicate that the association of UGT1A1*28 polymorphism to SN-38 concentration and to haematological toxicity appear to depend on the incoming load of SN-38 to be metabolised by UGT enzymes. The dose-dependent association of UGT1A1*28 and SN-38 or neutropenia observed with non-liposomal irinotecan administration is consistent with this hypothesis. Furthermore, liposomal encapsulation appears to spread out the incoming load of SN-38 by controlling the release of irinotecan. This is supported by a study in subjects with advanced gastric cancer in which 100 mg/m^2 irinotecan liposome injection administration resulted in five times lower plasma SN-38 C_{max} as compared to 300 mg/m^2 non-liposomal irinotecan (PEP0206) [Roy 2013]. Reduced load of SN-38 may allow for metabolism by UGT enzymes even in patients with reduced UGT enzyme activities (for example, UGT1A1*28 homozygous patients).

Despite the lack of associations between UGT1A1*28 homozygosity, safety, and PK, the irinotecan liposome injection USPI [Onivyde® USPI 2017] followed the NAPOLI-1 protocol that started homozygous patients at a lower dose due to the comparatively small number of patients with UGT1A1*28 homozygous treated with irinotecan liposome injection. Therefore, the absence of a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure or toxicity following irinotecan liposome injection administration warrants further study. In this study, the starting dose of irinotecan liposome injection will be the same

regardless of UGT1A1*28 genotype. UGT1A1*28 genotype will be collected on all subjects as a safety biomarker to further analyse the association between UGT1A1*28 homozygosity, SN-38 concentration and toxicity. Irinotecan liposome injection dose reduction will follow the same dose reduction rules for all subjects regardless of UGT1A1*28 genotype. Regular safety monitoring of subjects will be conducted by the sponsor medical monitor(s) and by the IDMC during the study. The safety and any available PK of UGT1A1*28 homozygous subjects will be compared to those who are non-homozygous for UGT1A1*28 to determine whether any different dosing strategy (such as a lower starting dose and/or different dose reduction for irinotecan liposome injection) is required for subjects who are homozygous.

2.2 Study Objectives

The primary objective of the study is to evaluate the efficacy of the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV versus nab-paclitaxel+gemcitabine in improving OS in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

The secondary objectives of the study are as follows:

- To evaluate progression free survival (PFS) according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 guidelines
- To evaluate the overall response rate (ORR) according to RECIST Version 1.1 guidelines
- To evaluate the safety of this regimen in this patient population.

The exploratory objectives of the study are as follows:

- To evaluate time to deterioration or worsening of subjects physical functioning, disease related symptoms and treatment related symptoms of interest using patient-reported outcome (PRO) data collected using the European Organisation for Research and Treatment of Cancer quality-of-life-core questionnaire (EORTC QLQ-C30) and, specific pancreatic cancer module (QLQ-PAN26) questionnaire and patient reported outcomes Common Terminology Criteria of Adverse Events (PRO-CTCAE) and the EuroQol 5 dimension health status questionnaire (5 level) (EQ-5D-5L)
- To evaluate the pharmacokinetics (PK), and the relationship between PK exposure and efficacy and safety, of the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV (Arm 1) in this patient population
- To compare time to treatment failure (TTF) between treatment arms
- To compare duration of response (DOR) between treatment arms
- To compare time to response (TTR) between treatment arms
- To describe the possible association between genotypes to include but not be limited to UGT1A1*28 and other UGT1A genotypes, SN-38 concentration (only for subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV) and safety
- To explore the pharmacodynamic biomarker CA 19-9 for the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV compared with nab-paclitaxel +gemcitabine in this patient population.
- To conduct biobanking of samples for future analysis of biomarkers amongst subjects who consent to optional biobanking.
- To collect gene mutation and genomic alteration status associated with pancreatic adenocarcinoma of subjects determined prior to screening (if available).

2.3 Study Hypothesis

Irinotecan liposome injection+oxaliplatin+5-FU/LV has superior efficacy over nab-paclitaxel+gemcitabine, demonstrated by a 3-month improvement in OS, in the treatment

of subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

3 STUDY DESIGN

3.1 General Design and Study Schema

This is an open-label, randomised, multicentre, phase III study to evaluate the efficacy and safety of the irinotecan liposome injection+oxaliplatin+5-FU/LV combination regimen versus nab-paclitaxel+gemcitabine in adult subjects with metastatic adenocarcinoma of the pancreas. After informed consent is obtained and subjects have been successfully screened, subjects will be randomised in a 1:1 ratio to one of the following treatment regimens:

- Arm 1: irinotecan liposome injection+oxaliplatin+5-FU/LV
- Arm 2: nab-paclitaxel+gemcitabine.

Approximately 750 subjects are planned to be randomised (1:1 approximately 375 subjects per arm).

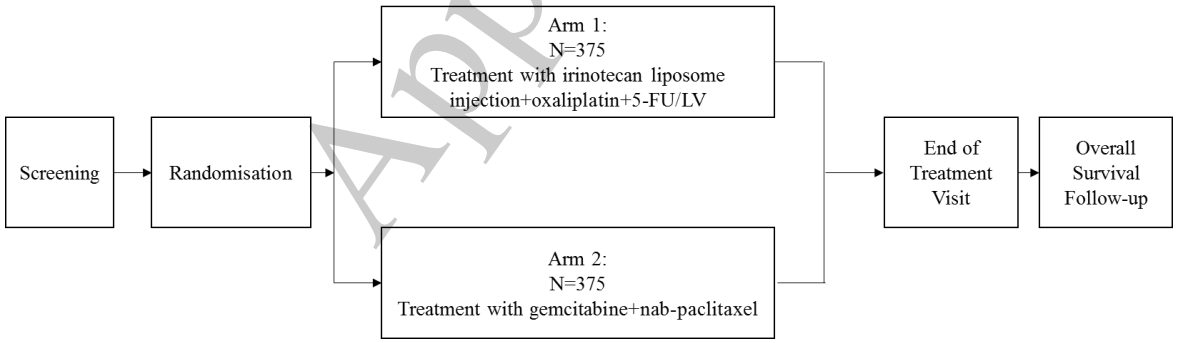
Subjects will be stratified according to:

- ECOG performance status (0/1)
- Region (North America/East Asia/Rest of the World)
- Liver metastases (Yes/No).

Dose adjustment is permitted as described in Section 3.6.

An IDMC will be established for this study to operate as an independent expert advisory group with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals (see Section 11.6).

Figure 2 Study Design



3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Efficacy Endpoint and Evaluations

The primary efficacy endpoint is the OS of subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV compared to subjects treated with nab-paclitaxel+gemcitabine.

Survival will be defined, in the standard way for OS evaluation, as time from the date of randomisation to the date of death (any cause). Subjects who do not have a date of death recorded at the time of the final analysis will be censored at the last known time that the subject was alive.

3.2.2 Secondary Efficacy Endpoint and Evaluations

3.2.2.1 Tumour Assessments

Tumour assessments are obtained by imaging, as described in Section 5.4.

Tumour response will be evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 [Eisenhauer 2009], to establish disease progression by computed tomography (CT) or magnetic resonance imaging (MRI) if the subject is allergic to CT contrast media. In addition, other imaging procedures, as deemed appropriate by the investigator, will be performed to assess sites of neoplastic involvement. The same method of assessment for each lesion must be used throughout the study. Investigators should select target and non-target lesions in accordance with RECIST Version 1.1 guidelines. Follow-up measurements and overall response should also be in accordance with these guidelines.

Tumour assessments should be completed until it has been determined that the subject has progressive disease (in accordance with RECIST Version 1.1). For subjects who do not have documented disease progression per RECIST Version 1.1 at the time of treatment termination, imaging studies should continue to be performed into the follow-up period every 8 weeks until radiological disease progression is documented or until the start of another anti-cancer treatment, whichever comes first. Continued imaging follow-up on schedule is recommended to reduce potential bias in the evaluation of the impact of the experimental treatments on disease [Fleming 2009].

The PFS is the time from randomisation to the first documented objective disease progression using RECIST Version 1.1 or death due to any cause, whichever occurs first. Determination of PFS will be per investigator assessment.

The ORR is defined as the proportion of subjects with a BOR characterised as either a complete response or partial response. BOR is defined as the best response as recorded from randomisation until documented objective disease progression using RECIST Version 1.1. To classify BOR as stable disease, there should be a qualifying stable disease assessment at least 8 weeks after randomisation. ORR of irinotecan liposome injection+oxaliplatin+5-FU/LV arm will be compared to the nab-paclitaxel+gemcitabine arm. Differences in ORR between Arm 1 and Arm 2 will be provided with 95% CIs and compared using a Cochran-Mantel-Haenszel test, adjusting by randomisation strata.

3.2.3 Safety Endpoints and Evaluations

3.2.3.1 Safety Assessments

Safety will be monitored through continuous reporting of AEs and serious adverse events (SAEs), laboratory abnormalities, incidence of subjects experiencing dose modifications (including infusion interruptions, dose omissions and dose delays) and/or premature discontinuation of study medication (and reason for discontinuation).

These safety evaluations will be performed from ICF signature, throughout the study to 30 days after the last study treatment administration (see Table 5).

3.3 Exploratory Endpoints

3.3.1 Patient-Reported Outcomes

The PRO exploratory endpoints are as follows:

- Assess time to deterioration or worsening of subjects physical functioning, disease related symptoms and treatment related symptoms of interest using the European Organisation for Research and Treatment of Cancer quality-of-life-core questionnaire (EORTC-QLQ-C30) and specific pancreatic cancer module (QLQ-PAN26) questionnaire and PRO of Common Terminology Criteria of Adverse Events (CTCAE)
- Assess time to deterioration or worsening on remaining quality of life (QoL) subscales of QLQ-C30 and QLQ-PAN26
- Compare % of subjects with stable, improved or worsened QoL scores as assessed by QLQ-C30, QLQ-PAN26 and PRO-CTCAE

- Summarise HRQoL score at each visit as assessed by QLQ-C30, QLQ-PAN26, PRO-CTCAE and EQ-5D-5L.

3.3.2 Pharmacokinetics

The pharmacokinetics (PK), and the relationship between PK exposure and efficacy and safety, of the regimen of irinotecan liposome injection+oxaliplatin+5-FU/LV (Arm 1) in this patient population will be evaluated.

3.3.3 Time to Treatment Failure

The time to treatment failure (TTF) between treatment arms will be compared. The TTF is defined as the time from randomisation to treatment discontinuation for any reason, including disease progression, treatment toxicity, subject preference, or death.

3.3.4 Duration of Response

Duration of response (DOR) is defined as the time of initial response (complete response or partial response) until documented tumour progression using RECIST guidelines Version 1.1 or death. For subjects who do not have documented tumour progression or death, DOR will be censored at the time of the last evaluable tumour assessment.

3.3.5 Time to Response

Time to response (TTR) will be computed only for subjects who achieved complete response or partial response. The TTR is the time from randomisation to the first objective tumour response.

3.3.6 Genotyping: UGT1A1 and SN-38

The possible association between genotypes to include but not limited to UGT1A1*28 and other UGT1A genotypes, SN-38 concentration (only for subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV) and safety will be described.

3.3.7 Biomarkers CA 19-9

The biomarker CA 19-9 will be measured and concentrations compared between treatment arms.

3.3.8 Biobanking

The exploratory endpoint comprises biobanking of samples for future analysis, among subjects who consent. Analysis of biobank samples will be performed outside the scope of the main study and reported separately.

Instructions for collection, processing, handling and shipment of the biobanking samples will be outlined in the laboratory manual.

3.3.9 Gene Mutations and Genomic Alterations

The exploratory endpoint comprises of collection of gene mutation and genomic alteration status associated with pancreatic adenocarcinoma of the subjects, determined prior to screening where available. Several genes are associated with an increased risk of developing PDAC. Those of key interest include:

- Germline mutations and genomic alterations: BRCA1, BRCA2, PALB2, ATM, CDKN2A, MLH1, MSH2, MSH6, TP53 and EPCAM [Rainone 2020].
- Somatic mutations and genomic alterations: KRAS, TP53, CDKN2A, SMAD4, RNF43, ARID1A, TGFβR2, GNAS, RREB1 and PBRM1 [Raphael 2017].

Gene mutations and genomic alteration may be used for exploration of potential predictive biomarkers and correlation with clinical outcome; the results may be reported separately.

3.4 Randomisation and Blinding

This is an open-label study and there is no blinding.

The sponsor's randomisation manager or a designee, who is a statistician independent from the study, will prepare a list of randomisation numbers. It will be produced in blocks, on a balanced ratio [1:1] and will be stratified according to:

- ECOG performance status (0/1)
- Region (North America/East Asia/Rest of the World)
- Liver metastases (Yes/No).

The randomisation and treatment arm assignation will be managed by interactive web response system (IWRS). After eligibility is confirmed, at Day 1 of Cycle 1 (or within 4 days prior to Cycle 1 Day 1 where required by local procedures) subjects will be assigned a randomisation number and to the associated treatment arm, in sequential order at each centre and within each level of strata.

The quantity of treatment kits will be also allocated by IWRS each time drug is dispensed, according to the allocated treatment group and subject body surface area (BSA). The IWRS will also manage all the logistical aspects of treatments (e.g. drug supplies, replacement of lost, damaged, quarantined, expiring and expired kits).

This service provides investigators, site co-ordinators and project team members with a 24-hour per day, 7-day per week service. In case of medical or technical randomisation or dispensation queries, a 24-hour helpline is available. See supporting information in the IWRS reference manual.

The investigator will under no circumstances change the randomisation number or the treatment group allocated to the subject. Recruitment will stop once approximately 750 subjects (or up to 800 subjects in the circumstance that over enrolment is necessary to meet 543 OS events, due to heavy censoring) have been randomised (see Section 11.2). However, subjects in screening at that time will be allowed to proceed in the study if they are eligible for entry, and subject data will be used in the analysis.

Randomised subjects who terminate their study participation for any reason before administration of the first dose of randomised study medication will retain their randomisation number (i.e. this number will not be reused). The next subject will be assigned another randomisation number, even if he/she should receive the same treatment. Subjects who leave the study early will not be replaced.

The sponsor's randomisation manager will keep the master randomisation list. A copy of this list will be also confidentially supplied to the IWRS vendor. The master list and the copy supplied to the IWRS vendor will be kept confidential in a secure location. Access to the randomisation list must be restricted until authorisation is given to release it for final analysis.

3.5 Maintenance of Randomisation and Blinding

This is an open-label study and there is no blinding.

3.6 Study Treatments and Dosage

Irinotecan liposome injection will be administered in combination with oxaliplatin and 5-FU/LV, as follows:

Arm 1: Doses and administration of irinotecan liposome injection, oxaliplatin, 5-FU/LV, on Days 1 and 15 of each 28-day cycle:

- Irinotecan liposome injection will be administered at 50 mg/m^2 (FBE) i.v. over 90 minutes (±10 minutes)
- Oxaliplatin will be administered at 60 mg/m^2 i.v. over 120 minutes (±10 minutes)

- LV (l+d racemic form-generic form) 400 mg/m^2, i.v. over 30 minutes (±5 minutes)
- 5-FU will be administered 2400 mg/m^2 i.v. over 46-hours (±120 minutes).

A more detailed description of administration procedures for Arm 1 is given in Section 6.2.1.

The comparator treatment will be administered as follows.

Arm 2: Doses and administration of nab-paclitaxel and gemcitabine (established doses as per USPI and EU SmPC nab-paclitaxel), on Days 1, 8 and 15 of each 28-day cycle:

- Nab-paclitaxel will be administered at 125 mg/m^2 i.v. over 35 minutes (±5 minutes)
- Gemcitabine will be administered at 1000 mg/m^2 i.v. over 30 minutes (±5 minutes).

A more detailed description of administration procedures for Arm 2 is given in Section 6.2.2.

For all drugs listed above a variation of 5% between the dose calculated by the IWRS and the total dose administered is permitted.

The label text for all study medication provided by the sponsor will be translated and/or adjusted, to be in compliance with applicable regulatory requirements (e.g. Good Manufacturing Practice guidelines (Volume 4 Annex 13)), national laws in force and in accordance with the local languages.

The investigator or designee will only dispense study medication to subjects included in this study. Each subject will only be given the regimen for the treatment group that the subject has been randomised to. The regimen administration for each subject will be documented in the electronic case report form (eCRF).

Both regimens are 28-day cycles unless cycle duration is modified by toxicity. (see Section 6.2.5 for details on dose modifications).

It is intended that subjects will be treated until radiologically determined progressive disease per RECIST Version 1.1 or unacceptable study medication related toxicity. However, a subject may discontinue study treatment at any other time (see Section 4.3.1).

3.7 Study Duration

For each subject, this study will consist of a 28-day screening period followed by 28-day cycles of treatment until radiologically determined progressive disease per RECIST Version 1.1, unacceptable study medication related toxicity or withdrawal from study. An EoT clinic visit is required approximately 30 days after last dose of study treatment to complete the final safety assessments of the treatment phase (see Section 8.1.4 for follow-up of AEs). Subsequently, subjects will be followed for survival once every 2 months via telephone, email, or clinic visit until death or study closure, whichever occurs first (see Section 4.3.3).

The subject's participation in the treatment phase of the study will be considered to have ended:

- at the time of the last visit
- in the case that the subject does not attend the last visit, 30 days after last study medication intake
- the death of the subject, if this occurs within 30 days after last study medication intake.

The overall duration of the study will be approximately 2.5 years. The study will be considered to have started when the first subject has provided signed informed consent.

The study will be completed once all subjects have discontinued the study treatment and at least 543 OS events have occurred in the randomised subjects.

3.8 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with FDA 21 CFR Part 11. As required by GCP guidelines, the sponsor assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, as a minimum, contain a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates, study medication administration and any AEs and associated concomitant medication.

As required by Section 6.4.9 of the International Conference on Harmonisation (ICH) Guideline E6(R2) [ICH E6(R2) 2016], if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the investigator and the sponsor.

Definition for source data and source documents are given below:

- **Source data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

The subject must have consented to their medical records being viewed by the sponsor's authorised personnel and by local and possibly foreign, competent authorities (CAs). This information is included in the subject's information and ICF.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

A subject will be eligible for inclusion in this study only if all the following criteria are met:

General Inclusion Criteria

(1) Subject has been informed about the nature of the study, and has agreed to participate in the study, and signed the ICF prior to participation in any study-related activities.

(2b) Male or non-pregnant and non-lactating female and ≥18 years of age:

(a) Females of child-bearing potential (i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy) must test negative for pregnancy at the time of screening based on a urine or serum pregnancy test. 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 postmenopausal 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. Female subjects of reproductive potential must agree to use a highly effective method of birth control, during the study and for 7 months following the last dose of study medication (see also Appendix 4 and Section 4.3.3).

(b) Male subjects must agree to use condoms during the study and for 6 months following the last dose of study medication.

Disease Specific Inclusion Criteria

(3) Histological or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting.

(4) Initial diagnosis of metastatic disease (as per American Joint Committee on Cancer 8th Edition [AJCC 2017]) must have occurred ≤6 weeks prior to screening.

(5a) Subject has one or more metastatic lesions measurable by CT scan (or MRI, if the subject is allergic to CT contrast media) according to RECIST Version 1.1 criteria.

(6a) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening and within 7 days prior to randomisation.

Haematological, Biochemical and Organ Function Inclusion Criteria

(7a) Subject has adequate biological parameters as demonstrated by the following blood counts:

(a) Absolute neutrophil count (ANC) ≥2000/mm^3 without the use of hemopoietic growth factors within the last 7 days prior to randomisation

(b) Platelet count ≥100,000/mm^3

(c) Haemoglobin (Hgb) ≥9 g/dL obtained ≤14 days prior to randomisation.

(8) Adequate hepatic function as evidenced by:

(a) Serum total bilirubin ≤1.5x upper limit of normal (ULN) (biliary drainage is allowed for biliary obstruction), and

(b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5x ULN (≤5x ULN is acceptable if liver metastases are present).

(9) Adequate renal function with a creatinine clearance (CL_{CR}) of >30 mL/min. Actual body weight should be used for calculating CL_{CR} using the Cockcroft-Gault Equation: CL_{CR}

(mL/min) = ((140–Age [years]) * (Weight [kg]/(Serum Creatinine [mg/dL]*72). Multiply the result by 0.85 if the subject is female. For subjects with a body mass index (BMI) >30 kg/m^2, adjusted body weight should be used instead.

(10a) Electrocardiogram (ECG) without any clinically significant findings (QT interval corrected by Fridericia's formula (QTcF) ≤450 msec and no known arrhythmias) and per the investigator's assessment.

(11) Adequate coagulation studies (obtained ≤14 days prior to randomisation) as demonstrated by prothrombin time and partial thromboplastin time within normal limits (≤1.5 x ULN). (Subjects on warfarin or other vitamin K antagonists should be discussed with the sponsor).

(12) Subject has no clinically significant abnormalities in urinalysis results (obtained within the last 7 days prior to randomisation), per the investigator's assessment.

(13) Subjects infected with human immunodeficiency virus (HIV) are eligible if they meet all the following criteria:

- (a) CD4 count is ≥350 cells/uL, viral load is undetectable, and not taking prohibited cytochrome (CYP)-interacting medications
- (b) Probable long-term survival with HIV if cancer were not present
- (c) Stable on a highly active antiretroviral therapy (HAART) regimen for ≥4 weeks and willing to adhere to their HAART regimen with minimal overlapping toxicity and drug-drug interactions with the experimental agents in this study
- (d) HIV is not multi-drug resistant
- (e) Taking medication and/or receiving antiretroviral therapy that does not interact or have overlapping toxicities with the study medication (Section 6.3.2).

4.2 Exclusion Criteria

Subjects must meet all the inclusion criteria listed above in Section 4.1 and none of the following exclusion criteria:

General Exclusion Criteria

(1) Any other medical or social condition deemed by the investigator to be likely to interfere with a subject's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.

(2a) Unwilling or unable to comply with study procedures and/or study visits, including long-term follow-up for survival.

Disease Specific Exclusion Criteria

(3) Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy:

- (a) Palliative radiotherapy is permitted
- (b) Placement of biliary stent/tube is permitted.

(4) Prior treatment of pancreatic adenocarcinoma with chemotherapy in the adjuvant setting, except those where at least 12 months have elapsed since completion of the last dose and no persistent treatment-related toxicities are present.

(5) Subject has only localised advanced disease.

(6a) Documented serum albumin <3 g/dL within 7 days prior to randomisation

(7) Known history of central nervous system (CNS) metastases. (Subjects on a stable or decreasing dose of steroids and deemed clinically stable as per the investigator's assessment are eligible).

(8) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, diarrhoea > Grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction.

(9) History of any second malignancy in the last 2 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Subjects with a history of other malignancies are eligible if they have been continuously disease free for at least 2 years prior to screening. Subjects who have a concurrent malignancy that is clinically stable and does not require tumour-directed treatment are eligible.

Haematological, Biochemical and Organ Function Exclusion Criteria

(10) Known hypersensitivity to any of the components of irinotecan liposome injection, other liposomal products, or any components of 5-FU, LV or oxaliplatin.

(11) Known hypersensitivity to any of the components of nab-paclitaxel or gemcitabine.

(12) Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including:

(a) Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening

(b) High cardiovascular risk, including, but not limited to, recent coronary stenting or myocardial infarction in the past year prior to screening

(c) New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure

(d) Known historical or active infection with hepatitis B, or active infection with hepatitis C (note that subjects with hepatitis C who have been clinically cured, defined as persistent absence of hepatitis C RNA detected by polymerase chain reaction (PCR) test in serum 12 weeks after completing antiviral treatment, are eligible for this study)

(13) Active infection or an unexplained fever >38.5°C during screening visits or on the first scheduled day of dosing (at the discretion of the investigator, subjects with tumour fever may be enrolled), which in the investigator's opinion might compromise the subject's participation in the study or affect the study outcome.

(14) Major surgery, other than diagnostic surgery, within 4 weeks prior to randomisation.

(15) Use of strong inhibitors or inducers of CYP3A, CYP2C8 and UGT1A1 (please refer to Appendix 1 and Section 6.3.2). Subjects are ineligible if:

- they are unable to discontinue the use of strong inhibitors of CYP3A, CYP2C8 and UGT1A1 at least 1 week prior to randomisation
- they are unable to discontinue the use of strong CYP3A and CYP2C8 inducers at least 2 weeks prior to randomisation.

(16) There is presence of any contraindications outlined in the Contraindications or Warnings and Precautions sections of the IB for irinotecan liposome injection, or in the prescribing information for 5-FU, LV or oxaliplatin.

(17) There is presence of any contraindications outlined in the Contraindications or Special Warnings and Precautions sections of the product prescribing information for nab-paclitaxel or gemcitabine.

(18) Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma.

(19) Subjects who, in the opinion of the investigator, have symptoms or signs suggestive of clinically unacceptable deterioration of the primary disease at the time of screening.

(20a) History of systemic connective tissue disorders (e.g. lupus, scleroderma, arteritis nodosa).

(21) History of interstitial lung disease, history of slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.

(22) History of peripheral artery disease (e.g. claudication, Leo Buerger's disease).

(23) Subjects who have received a live vaccine within 4 weeks prior to randomisation.

(24) Known low or absent dihydropyrimidine dehydrogenase (DPD) activity. Where required by local regulations, testing for DPD deficiency must be performed using a validated method which is recommended by local health authorities.

4.3 Stopping Rules, Discontinuation and Withdrawal Criteria and Procedures

4.3.1 Discontinuation of Study Treatment

It is intended that subjects will be treated until radiologically determined progressive disease per RECIST Version 1.1 or unacceptable study medication related toxicity. However, a subject may discontinue study treatment at any other time. Reasons for discontinuation of study treatment include, but are not limited to the following:

- Radiologically determined progressive disease, per RECIST Version 1.1
- Clinical deterioration sufficient to prevent further radiological assessment
- A study medication related AE, prior to disease progression, which:
  - in the opinion of the investigator, precludes further treatment with all study medication
  - requires treatment regimen to be withheld (see maximum durations described in Section 6.2.5), unless in the opinion of the investigator the subject is receiving benefit overall from the study treatment
  - would result in more dose reductions than allowed in the study protocol (details can be found in Appendix 2 and 3
  - requires discontinuation of irinotecan liposome injection, 5-FU or LV in Arm 1 or nab-paclitaxel or gemcitabine in Arm 2
- Development of an intercurrent medical condition or need for concomitant therapy that precludes further treatment with all study medications
- Withdrawal of consent for further treatment
- Withdrawal of consent for further treatment and survival follow-up
- Discretion of the treating physician
- Pregnancy.

Subject may be permitted to continue study treatment after RECIST v1.1 criteria for progressive disease are met if in the investigator's opinion that subject is receiving clinical benefit from study treatment. Documented evidence of clinical benefit must include all of the following criteria: absence of symptoms and signs (including worsening of laboratory values) indicating unequivocal progression of disease, meaningful reduction from baseline of tumour biomarker CA19-9, and no decline in ECOG performance status. At the time of initial progression investigator must discuss with the subject deferring any standard treatment options and possibility of continuing study treatment. Decision made by the investigator and the subject should be documented in the clinic notes. Investigator must receive written sponsor or sponsor's delegate approval before subject with radiologically confirmed progressive disease by RECIST v1.1. continues any study treatment.

Dosing may be delayed from when it was scheduled (permitting a total of 28 days between the scheduled Day 1 and Day 15 doses for Arm 1 and up to 21 days for Arm 2, Section 6.2.5 – note that Arm 2 has scheduled Day 1, Day 8 and Day 15 dosing and the maximum delay between a missed scheduled dose and the next one, whichever dose was missed, should not be longer than 21 days) to allow for recovery from toxicity related to the study treatment. If the time required for recovery from toxicity is more than described in Section 6.2.5, consideration should be given to discontinuing the subject from further treatment, unless the subject is demonstrating benefit overall, in which case the possibility of remaining on study medication should be discussed between investigator and sponsor, or delegate after review of the associated risks and benefits. However, if oxaliplatin is not well tolerated in subjects randomised to Arm 1, oxaliplatin may be discontinued and subjects may continue to receive irinotecan liposome injection+5-FU/LV at the discretion of the investigator and continue in the study (see Sections 6.2.1 and 6.2.5.1). Toxicity requiring discontinuation of any of the drugs in either regimen (apart from oxaliplatin) will result in discontinuation from the study treatment.

An EoT clinic visit is required approximately 30 days after last dose of study treatment to complete the final safety assessments. Subsequently, subjects will be followed for survival once every 2 months via telephone, email, or clinic visit until death or study closure, whichever occurs first. A subject who discontinues study medication but has not withdrawn from the study should also continue the disease evaluation assessment (CT/MRI) until confirmed radiographic disease progression as described in Section 5 or until the subject starts alternative anti-cancer therapy, whichever comes first.

4.3.2 Withdrawal from the Study

Reasons for withdrawal from treatment, but continuation in follow-up in the study are described in Section 4.3.1. Withdrawal from the study (including withdrawal from both treatment and follow-up) include, but are not limited to the following:

- Death of the subject
- Subject is lost to follow-up (see Section 4.3.3)
- Withdrawal of consent
- Study termination by the sponsor
- Significant noncompliance with the protocol, per investigator's assessment.

4.3.3 Procedures Following Study Medication Discontinuation or Study Withdrawal

The date the subject discontinues study treatment or withdraws from the study, the primary reason for study treatment discontinuation, study termination, and/or termination of participation (e.g. withdrawal of consent) will be captured within the eCRF.

Following study medication discontinuation all procedures and evaluations required at the 30-day EoT visit should be completed. All subjects who discontinue study medication as a result of an AE must be followed until resolution or stabilisation of the AE. Subjects who discontinue study medication prior to radiologically determined disease progression should continue to be assessed radiologically, according to the protocol-specified schedule, until radiologically determined progressive disease per RECIST Version 1.1, has been documented or until the subject starts alternative anti-cancer therapy, whichever comes first.

Subjects are instructed to continue using highly effective methods of birth control (females) and condoms (males) for the duration of the study and for 7 months (females) and 6 months (males) months after receiving the last dose of any study treatment.

The OS follow-up contacts should continue every 2 months from the 30-day EoT visit until death or study closure, whichever comes first. If a subject does not return to the clinic or respond to follow-up visit telephone calls, attempts should be made to contact the subject or their family

via phone, email, or mail. At least three documented attempts, including one via certified mail, should be made to contact the subject before declaring a subject potentially lost to follow-up. If the subject is considered potentially lost to follow-up, the date of death may be captured from public records or all other means allowed per local regulations. No subject can be considered as lost to follow-up before final study closure.

If a subject withdraws from the study treatment at any point, a complete final evaluation at the time of the subject's withdrawal should be made with an explanation of the reason for withdrawal. At the time of discontinuation from the study treatment, it should be clarified with the subject that they will continue to be assessed radiologically, according to the protocol-specified schedule, until radiologically determined progressive disease per RECIST Version 1.1, has been documented or until the subject starts alternative anti-cancer therapy, whichever comes first.

Afterwards, the subject will be followed up for survival status (including where appropriate through publicly available records).

Subjects participating to the optional research biobanking program have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. the entire 15 years during which the sample is kept). If a subject wishes to withdraw consent for biobanking, and the samples are still at the investigator site or at the central laboratory at this time, the investigator must inform the study monitor in writing of the subject's decision and destroy the samples. If the samples are in the sponsor's central biorepository, the investigator must inform Ipsen directly of the withdrawal using the e-mail address, CCI, mentioning only the patient ID in this e-mail. Ipsen will ensure the destruction of the samples and all corresponding aliquots and issue confirmation of the destruction, which will be forwarded to the investigator. Analyses conducted before withdrawal will not be affected.

4.3.4 Study Termination

The sponsor reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrolment
- Safety concerns
- Drug supply or manufacturing issues
- The sponsor's decision to modify or discontinue the development of irinotecan liposome injection
- A request to discontinue the study by the relevant regulatory authorities.

The sponsor will promptly inform all investigators and the relevant regulatory authorities if the study is suspended or terminated for any reason. The investigator will promptly notify their IRB/EC if the study is suspended or terminated.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 5.

If the COVID-19 pandemic prevents subjects from coming to the site, subjects can have their study visit assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor (or delegate) before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort to confirm all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments is provided in Appendix 8. Independent ethics committees (IECs)/institutional review boards (IRBs) will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

Table 5 Study Procedures and Assessments

	Screening	Treatment Phase: 28 Day cycle (unless modified due to toxicity)										Follow-up Phase	
		Cycle 1					Additional Cycles						
	D-28 to Randomisation	D1	D3 (A1)	D8 (A2)	D15	D17 (A1)	D1	D3 (A1)	D8 (A2)	D15	D17 (A1)	Q8W after randomisation	EoT Visit (30±14 days after last dose)	Q2M after EoT visit
Informed consent[a]	X													
Eligibility[b]	X													
Randomisation[c]		X												
Medical history[d]	X													
Demographics[d]	X													
Vital signs, physical exam[e]	X	X			X		X			X			X	
ECOG performance status[f]	X	X		X	X		X		X	X			X	
QLQ-C30, QLQ-PAN26, EQ-5D-5L[g]		X					X						X	
PRO-CTCAE[g]		X			X		X			X			X	
ECG[h]	X	X			X(A1)		X(A2)						X	
Haematology [i]	X	X		X	X		X		X	X			X	
Blood biochemistry[j]	X	X		X	X		X		X	X			X	
Urinalysis[j]	X													
UGT1A1*28 [k]	X													
DPD testing [z]	X													
CA19-9[l]	X	X					X[l]							
Pregnancy test [m]	X	X					X						X	
Plasma for PK (Arm 1 only) [n]		X	X		X									
Disease evaluation (CT/MRI) [o]	X											X	X	X
Pre-medication/ Check blood results[p]		X		X	X		X		X	X				
Arm 1: Nal-IRI +oxaliplatin +5-FU/LV [q]		X			X		X			X				
Arm 1: Removal of 5-FU pump [r]			X			X		X			X			

	Screening	Treatment Phase: 28 Day cycle (unless modified due to toxicity)										Follow-up Phase	
	D-28 to Randomisation	Cycle 1					Additional Cycles					Q8W after randomisation	EoT Visit (30±14 days after last dose)	Q2M after EoT visit
		D1	D3 (A1)	D8 (A2)	D15	D17 (A1)	D1	D3 (A1)	D8 (A2)	D15	D17 (A1)			
Arm 2: gemcitabine +nab-paclitaxel [s]		X		X	X		X		X	X				
Prior and concomitant meds and procedures[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE/SAEs [v]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Overall survival [w]														X
Further anticancer therapy [w(i)]														X
Archival tumour tissue[x]	X													
Biobanking blood and stool [y]		X					X[y]						X	

Abbreviations and Footnotes

Note: All cycles are 28-day cycles, unless modified due to toxicity

Note: pre-dose assessments can be completed 2 days prior to dosing according to local standard of care

5-FU=5-flurouracil, A1=Arm 1, A2=Arm 2, AE=adverse event, βHCG=β human chorionic gonadotropin, BSA=body surface area, C=cycle, CT=computed tomography, D=day, DNA=deoxyribonucleic acid, DPD= Dihydropyrimidine dehydrogenase, ECG=electrocardiogram, EORTC= European Organisation for Research and Treatment of Cancer, EoT=End of Treatment, EQ-5D-5L=EuroQol 5 dimension health status questionnaire (5 level), HRQL= health-related quality of life, Nal-IRI=irinotecan liposomal injection, LV=leucovorin, MRI=magnetic resonance imaging, OS=overall survival, QLQ-PAN26=quality of life questionnaire pancreatic cancer module, PK=pharmacokinetics, QLQ-C30=quality-of-life core 30 questionnaire, Q2M=every 2 months, Q8W=every 8 weeks, RECIST= Response Evaluation Criteria in Solid Tumours, RNA=ribonucleic acid, SAE=serious adverse event, SmPC=summary of product characteristics.

a **Informed consent**: Informed consent to be signed before any screening activities take place. Additional optional biobanking informed consent to be signed for subjects who are willing to participate in the biobanking sampling.

b **Eligibility**: To be checked against the inclusion and exclusion criteria.

c **Randomisation**: Only to be performed when a subject has been successfully screened. Randomisation to be performed on C1D1, or within 4 days prior to C1D1 where required by local procedures. Date of randomisation must be entered in the eCRF.

d **Medical history and demographics**: To be completed during the screening process i.e. within 28 days prior to randomisation. Gene mutation status and genomic alterations of the subjects determined prior to screening will be collected at Screening (if available) and will be recorded as part of the disease history in the eCRF (See Section 3.3.9 for list of associated genes for collection).

e **Vital signs and physical examination**: Procedures to be completed within 7 days prior to randomisation. Vital signs will include height (at screening only) weight, resting blood pressure, pulse and temperature. BSA is calculated within 2 days before D1 and D15 of each cycle before treatment administration. Physical examination must include neurological examination on D1 of each cycle.

f **ECOG performance status**: To be assessed within 7 days prior to randomisation.

g **HRQL questionnaires:** On D1 of treatment cycles, HRQL questionnaires must be completed before study treatment administration.
Note: Every effort should be made for the QoL to be completed within 24 hours prior to the planned visit date. QoL does not need to be repeated if the QoL was completed on the planned

visit date and the visit was subsequently postponed. If a subject is unable to complete the QoL on the planned visit date, then this can be performed on the new postponed visit date. QoL should always be completed prior to study assessments.

h **ECG**: For screening, ECG to be measured within 28 days prior to randomisation. Arm 1 only: ECG to be performed pre and post oxaliplatin infusion on D1 and D15 of C1 only and repeated as clinically indicated during the study. Arm 2 only: ECG to be performed pre infusion of nab-paclitaxel and gemcitabine on D1 of Cycles C1, C2, C3 and C4 and repeated as clinically indicated during the study. In addition, ECG to be repeated as clinically indicated during the study.

i **Haematology**: For the screening sample, collection should occur within 7 days before randomisation. Routine or historical samples taken before signing ICF within this timeframe can be used for the screening sample. Day 8 collections are required for Arm 2 only. Results of samples taken must be obtained and reviewed prior to dosing (D1, D8 and D15**).** Refer to Section 8.2.1 for the required results, e.g. coagulation testing.

j **Biochemistry and Urinalysis**: For the screening sample, collection should occur within 7 days before randomisation. Serum biochemistry must be assessed centrally but can also be analysed locally in the case of requiring timely results for medical management. Screening central biochemistry results must be obtained prior to randomisation. Urinalysis will be performed locally. Refer to the eCRF completion guideline for the required results.

k **UGT1A1*28**: Sample to be collected within 7 days prior to randomisation. Biomarker result not required prior to enrolment in the study or prior to dosing on C1D1.

l **CA19-9**: First sample to be collected within 7 days prior to randomisation. Sample to be collected at D1 of every other cycle, i.e. C1D1, C3D1, C5D1, etc.

m **Pregnancy test (urine or serum βHCG)**: Sample to be collected and results reviewed prior to randomisation and before treatment on D1 of each cycle. Any positive urine pregnancy test must be confirmed via serum β-HCG.

n **PK sampling (Arm 1 only)**: C1D1: Samples collected at the following timepoints: pre-dose (within 24 hours prior to irinotecan liposome injection infusion); at the end of the irinotecan liposome injection infusion (+15 mins) and at the end of the oxaliplatin infusion (+5 mins). C1D3: Sample collected within 2 hours prior to the completion of the 5-FU infusion. C1D15: Sample collected just prior to dosing with irinotecan liposome injection (within 24 hours). If subject is seen in clinic between C1D3 and C1D15 then an additional PK sample should be collected at the time of the visit (subject does not need to come to clinic for this sample only).

o **Disease evaluation**: For screening to be performed within 28 days before randomisation. CT (or MRI if the subject is allergic to CT contrast media) according to RECIST Version 1.1. Routine or historical scans taken before signing ICF within this timeframe can be used to perform the screening assessment according to RECIST Version 1.1. Scan schedule is Q8W after randomisation. The scan schedule of every 8 weeks (± 7 days) after randomisation is to be adhered to, regardless of whether the subject has a treatment delay. EoT visit: Disease evaluation to be performed unless completed in the 8 weeks before the EoT visit. Q2M after EoT visit: For subjects who discontinue the study treatment for reasons other than radiologically confirmed disease progression per RECIST version 1.1 and have not started any further anti-cancer treatment (e.g. subjects who are removed due to adverse events).

p **Pre-medication Arm 1**: Dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics. Atropine may be prescribed as per standard of care and/or prophylactically for subjects who experienced acute cholinergic symptoms. **Arm 2:** As per standard practice or Prescribing Information/SmPC. Prior to each dosing for Arm 1 and prior to each cycle for Arm 2, subjects must comply with the relevant blood count criteria (see Section 6.2.3).

q **Arm 1: Nal-IRI +oxaliplatin+5-FU/LV**: Infusions to be administered ±2 days from scheduled date of administration in the following order: irinotecan liposome injection, followed by oxaliplatin infusion, followed by LV (30 minutes after oxaliplatin end) and then 5-FU infusion (within 60 minutes after LV). On D1 of every cycle, treatment experience during the previous cycle(s) will be reviewed in case dose modification(s) are required.

r **Arm 1: Removal of 5-FU pump**: Pump removal might occur at a home visit, rather than a visit to site except at C1D3. For C1D3 the subject will visit the site and a PK sample will be taken 2 hours before the pump finishes delivering 5-FU. Time of PK sample and time of finishing pump infusion must be recorded.

s **Arm 2: gemcitabine+nab-paclitaxel**: Infusions to be administered ±2 days from scheduled date. There must always be at least 6 days between Day 1 and Day 8 and Day 8 and Day 15. Administration in the following order: administration of nab-paclitaxel first, followed by gemcitabine. On D1 of every cycle, treatment experience during the previous cycle(s) will be reviewed in case dose modification(s) are required.

u **Prior and concomitant medications and procedures**: To be recorded in the eCRF during the screening period (i.e. within 28 days before randomisation) and then as an ongoing process throughout the study.

v **AEs/SAEs**: Subjects must be followed for AEs/SAEs, regardless of relationship, from the time they signed the informed consent until at least 30 days after the last dose of study treatment.

w **Overall survival**: Follow-up contacts should be made Q2M (±7 days) until death or study completion; data collected should include OS status.

w(i) **Further anticancer therapy**: Follow-up contacts should be made Q2M (±7 days) until death or study completion; data collected should include any subsequent anti-cancer treatment information.

x **Biobanking: Archival tumour samples**: Archived samples to be collected for those individuals who have signed the optional biobanking informed consent.

y **Biobanking: Blood and stool:** Only to be collected for those individuals who have signed the optional biobanking informed consent. Whole blood (samples for RNA, circulating free DNA, plasma), and stool samples will be collected prior to treatment dosing on C1D1 and every other cycle after that (i.e. C3D1, C5D1, etc). Whole blood for DNA samples will be collected on C1D1 only.

z **DPD testing**: Where required by local regulations, testing for DPD activity must be performed using a validated method which is recommended by local health authorities (Appendix 7). Result to be received and reviewed prior to randomisation.

5.2 Study Visits

5.2.1 Procedures for Screening and Enrolment

The screening phase will begin once the subject signs the ICF. All procedures for screening are outlined in Table 5.

For further descriptions of the clinical and laboratory assessments required, please refer to Section 8.2.

Subjects will be offered to participate in an optional research biobanking programme. Subjects who agree to participate will be requested to sign a separate informed consent. Subjects can participate in the study even if they are not participating in the optional biobanking programme.

After informed consent is obtained, all subjects will be allocated a subject number. Screened subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

Under no circumstances will subjects be screened more than once, however, on discussion with the sponsor medical monitor (or delegate), it may be required that some assessments need to be repeated, such as safety assessments and blood sampling.

Following confirmation of eligibility for the study, subjects will be given a randomisation number and allocated to one of the dosing groups specified in Section 3.6.

In the event that the subject does not receive study medication, the primary reason will be recorded.

5.2.2 Procedures During Study Treatment Phase

Procedures will be performed during the study treatment phase as per Table 5.

5.2.3 Procedures After Study Treatment (Follow-up Phase)

5.2.3.1 End of Treatment Visit

Subjects will continue to receive treatment until radiologically determined progressive disease per RECIST Version 1.1, unacceptable study medication related toxicity or withdrawal. An EoT visit is required approximately 30 days (±14 days) after last dose of study treatment to complete the final safety assessments.

For subjects who withdraw prematurely from the study, final evaluations will be performed at the EoT visit (30±14 days after the last dose).

Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.4 and Section 8.1.2.5, respectively.

All procedures and assessments are outlined in Table 5.

Subjects are to use contraception throughout the study, as well as after they stop receiving study medication, as described in Section 4.3.3.

5.2.3.2 Follow-up Visits

After the EoT visit, subjects should continue to be followed for survival status once every 2 months (±7 days) via telephone, email, clinic visit, or medical record review until death, withdrawal of consent or study closure, whichever occurs first. Additionally, data on subsequent anti-cancer treatments should be collected during these contacts and documented in the eCRF. In the case of subjects who are discontinued from treatment for reasons other than progressive disease per RECIST Version 1.1, disease evaluations (including imaging studies) should continue into the follow-up period, as described in Section 4.3.3.

If a subject does not respond to the OS follow-up contacts, at least three documented attempts, including one via certified mail, should be made to contact the subject before declaring a subject potentially lost to follow-up. If the subject does not respond to these requests, the date of death may be captured from public records or all other means allowed by local regulations.

5.3 Laboratory Assessments

The total volume of blood drawn for all evaluations throughout this study is dependent on the numbers of cycles of treatment completed and is estimated in Table 6 (see Section 10 for biobanking sample volumes, which are not included in this estimate).

Table 6 Estimates of Blood Volume Drawn Throughout the Study

Study Phase	Arm 1	Arm 2
Screening	20 mL	20 mL
Cycle 1	70 mL	25 mL
Per subsequent cycle	20 mL	25 mL
Pregnancy test for women (Screening and Day 1 of each cycle)	3.5 mL per test	3.5 mL per test

Notes: Estimates given to the nearest +5mL
An additional 16.5 to 19 mL of blood will be collected from subjects who have signed the optional biobanking informed consent.

Technical instructions will be provided in a separate laboratory manual.

The following samples will be analysed locally:

- Haematology samples will be assessed at the site's local laboratory (see Section 8.2.1)
- Blood biochemistry samples can be assessed at the site's local laboratory only if needed to allow for immediate decision-making (see Section 8.2.2 and also note that centrally assessed biochemistry results are required to confirm eligibility). Blood biochemistry samples will be assessed at central laboratory (in the list below).
- Dipstick urinalysis
- Pregnancy test (see Section 8.2.5).
- DPD testing will be performed using a validated method which is recommended by local health authorities at the site's local laboratory (See Section 8.2.7 and Appendix 7).

The following samples will be sent for central analysis:

- Blood biochemistry (see Section 8.2.2)
- CA19-9 (see Section 8.2.4)
- UGT1A1*28 (see Section 8.2.3)
- PK samples (see Section 9.1).

5.4 Imaging

Subjects will have CT scans (or MRI if the subject is allergic to CT contrast media) performed every 8 weeks (see Table 5) that will be evaluated by the investigator using RECIST guidelines Version 1.1 for complete response, partial response, stable disease or progressive disease.

The sponsor will collect and store all tumour assessment images for all subjects throughout the study.

For subjects who discontinue the study treatment for reasons other than radiologically confirmed disease progression per RECIST version 1.1 and have not started any further anti-cancer treatment, will have follow-up Q2M after EoT for disease evaluation.

Technical instructions will be provided in separate image acquisition guidelines.

The CT scans (or MRI) will be retained by the sponsor for central independent assessment, should this be required.

6 TREATMENT OF SUBJECTS

6.1 Study Medication Preparation, Storage, Security and Accountability

All medication provided to the subject (i.e. irinotecan liposome injection, oxaliplatin, 5-FU, LV, nab-paclitaxel and gemcitabine) is classed as study medication. The study medication that is provided to the clinical site by the sponsor is also referred to as IMP. All IMP is study medication but not all study medication may be defined as IMP.

6.1.1 Study Medication Storage and Security

The investigator or an approved representative (e.g. pharmacist) will ensure that all study medication (i.e. irinotecan liposome injection, oxaliplatin, 5-FU, LV, nab-paclitaxel and gemcitabine) is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements and the pharmacy manual.

Temperature of storage for irinotecan liposome injection is described in Section 6.2.1.1 and accompanying packaging information provides the relevant storage conditions for the other study medications.

6.1.2 Investigational Medicinal Product Preparation

The investigator or an approved representative (e.g. pharmacist) will ensure that all study medication is prepared and dispensed by qualified staff members.

6.1.3 Investigational Medicinal Product Accountability

All IMP sourced by the sponsor is to be accounted for in the Drug accountability module within the IWRS system.

The investigator, institution or the head of the medical institution (where applicable) is delegated by the sponsor to be responsible for IMP accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records). The sponsor will provide guidance on the destruction of unused IMP. If destruction is authorised to take place at the investigational site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by the sponsor. All destruction must be adequately documented. Further guidance and information for the receipt, preparation, management, disposal and return of the IMP are provided in the "Investigational Medicinal Product Handling Manual".

6.2 Study Medications Administered

At screening, subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be allocated to one of the following treatment groups:

- Arm 1: irinotecan liposome injection+oxaliplatin+5-FU/LV

or

- Arm 2: nab-paclitaxel+gemcitabine

6.2.1 Irinotecan Liposome Injection+Oxaliplatin+5-FU/LV (Arm 1)

Prior to the infusions contained in Arm 1 all subjects must be pre-medicated as detailed in Section 6.3.1. The order of the infusions to be administered in the clinic is as follows: irinotecan liposome injection, followed by oxaliplatin infusion, followed by LV and then 5-FU infusion. (Refer to study schedule Table 5).

Arm 1: Doses and administration of irinotecan liposome injection, oxaliplatin, 5-FU/LV on Days 1 and 15 of each 28-day cycle:

- Irinotecan liposome injection will be administered at 50 mg/m^2 i.v. over 90 minutes (±10 minutes)

- Oxaliplatin infusion, after completion of irinotecan liposome injection, will be administered at 60 mg/m^2 i.v. over 120 minutes (±10 minutes). Note that oxaliplatin may be omitted due to toxicity (see Section 6.2.5.1 for dose modification to an alternative regimen without oxaliplatin for Arm 1 in the case of toxicity).
- LV (l+d racemic form-generic form) infusion will start 30 minutes (+10 minutes) after completion of oxaliplatin administration, at 400 mg/m^2, i.v. over 30 minutes (±5 minutes)
- 5-FU infusion will start within 60 minutes after completion of LV administration, at 2400 mg/m^2 i.v. over 46-hours (±120 minutes).

  As the infusion of 5-FU is administered over 46 hours the subject will go home with an administration pump. The subject will either need to return to the clinic at the end of infusion for removal of the pump or, alternatively, if possible, arrangements might be made for the pump to be removed at the subject's home (except on Cycle 1 Day 3).

6.2.1.1 Irinotecan Liposome Injection, Dose, Mode of Administration:

Irinotecan liposome injection is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for i.v. infusion. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrosofate salt. It is supplied in sterile, single-use vials containing 10 mL of irinotecan liposome injection at a concentration of 4.3 mg/mL free base equivalent (FBE).

Irinotecan liposome injection must be stored refrigerated (2 to 8°C, 36 to 46°F) with protection from light and must not be frozen.

Responsible individuals should inspect vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe. They must contact the sponsor or its designee if they notice a problem with the study medication.

Irinotecan liposome injection must be diluted prior to administration. Because of possible microbial contamination during dilution, the diluted solution should be used immediately, but the diluted solution may be stored at room temperature (15 to 25°C) for up to 4 hours prior to infusion or may be refrigerated (2 to 8°C) for up to 24 hours prior to use. Diluted solution must be protected from light prior to infusion. The diluted solution must not be frozen. Further instructions are provided in the pharmacy manual.

6.2.1.2 Oxaliplatin, Leucovorin, 5-Fluorouracil

Commercial oxaliplatin, LV and 5-FU are provided by the sponsor. This could be supplied by the site where allowed by local regulations, but only when approved by the sponsor. Sponsor-sourced commercial oxaliplatin, LV and 5-FU will be labelled in accordance with local country requirements. Instructions for storage and handling are provided in the pharmacy manual. For commercial treatment supplied locally, all information related to the product administered must be reported in source documentation and entered in the eCRF in accordance with the requirements stated in the eCRF completion guidelines.

6.2.2 Nab-paclitaxel+Gemcitabine (Arm 2)

Arm 2: Doses and administration of nab-paclitaxel+gemcitabine (established doses as per USPI nab-paclitaxel) On Days 1, 8 and 15 of each 28-day cycle:

- Nab-paclitaxel will be administered at 125 mg/m^2 i.v. over 35 minutes (±5 minutes)
- Gemcitabine will be administered at 1000 mg/m^2 i.v. over 30 minutes (±5 minutes)

6.2.2.1 Nab-paclitaxel and Gemcitabine

Commercial gemcitabine and nab-paclitaxel are provided by the sponsor. This could be supplied by the site where allowed by local regulations, but only when approved by the sponsor.

Sponsor-sourced commercial gemcitabine and nab-paclitaxel will be labelled in accordance with local country requirements. Instructions for storage and handling are provided in the pharmacy manual. For commercial treatment supplied locally, all information related to the product administered must be entered in the eCRF in accordance with the requirements stated in the eCRF completion guidelines.

6.2.3 Combination Therapy Study Cycles

Both regimens are 28-day cycles unless cycle duration is modified by toxicity.

The toxicity of each dose must be recorded prior to the administration of a subsequent dose and graded according to the National Cancer Institute (NCI) CTCAE (Version 5.0). All dose modifications for all arms should be based on the worst preceding toxicity. Dose modification details are given in Section 6.2.5.

- Arm 1: irinotecan liposome injection+oxaliplatin+5-FU/LV
  Prior to each **dosing**, subjects must have:
  - ANC ≥2000/mm^3
  - Platelet count ≥100,000/mm^3
  - Diarrhoea ≤ Grade 1.
- Arm 2: nab-paclitaxel+gemcitabine
  Prior to each **cycle**, subjects must have:
  - ANC ≥1500/mm^3
  - Platelet count ≥100,000/mm^3
  - Diarrhoea ≤ Grade 1.

Dosing may be delayed as detailed in Section 6.2.5, to allow for recovery from toxicity. If the subject does not recover this may lead to discontinuation of study treatment (see Section 4.3 for details). However, if oxaliplatin is not well tolerated in subjects randomised to Arm 1, oxaliplatin may be discontinued and subjects may continue to receive irinotecan liposome injection+5-FU/LV at the discretion of the investigator and continue in the study. Toxicity requiring discontinuation of any of the drugs in either regimen (apart from oxaliplatin) will result in discontinuation from the study treatment (see Section 4.3 and Section 6.2.5).

6.2.4 Management of Infusion Reactions

The guidelines described in this section can be followed in case of infusion reactions to any study treatment in either arm given per protocol. Infusion reactions will be defined according to the NCI-CTCAE (Version 5.0) definitions of an allergic reaction or anaphylaxis as defined below:

6.2.4.1 Allergic Reaction

An allergic reaction is a disorder characterised by an adverse local or general response from exposure to an allergen:

- Grade 1: Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated
- Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤ 24 hrs
- Grade 3: Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)

- Grade 4: Life-threatening consequences; urgent intervention indicated.

6.2.4.2 Anaphylaxis

Anaphylaxis is a disorder characterised by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death):

- Grade 1: Not applicable
- Grade 2: Not applicable
- Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/angioedema; hypotension
- Grade 4: Life-threatening consequences; urgent intervention indicated.

6.2.4.3 Treatment Guidelines

Institutional policies or the following treatment guidelines shall be used for the management of infusion reactions.

(1) Grade 1:
- Slow infusion rate by 50%
- Monitor subject every 15 minutes for worsening of condition
- Future infusions may be administered at a reduced rate (e.g. over 120 minutes for irinotecan liposome injection), at the discretion of the investigator.

(2) Grade 2:
- Stop infusion
- Administer diphenhydramine hydrochloride 50 mg i.v., acetaminophen 650 mg orally, and oxygen
- Resume infusion at 50% of the prior rate once infusion reaction has resolved
- Monitor subject every 15 minutes for worsening of condition
- For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 50 mg i.v., dexamethasone 10 mg i.v., and acetaminophen 650 mg orally
- Future infusions may be administered at a reduced rate (e.g. over 120 minutes for irinotecan liposome injection), at the discretion of the investigator.

(3) Grade 3:
- Stop infusion and disconnect infusion tubing from subject
- Administer diphenhydramine hydrochloride 50 mg i.v., dexamethasone 10 mg i.v., bronchodilators for bronchospasm, and other medications or oxygen as medically necessary
- No further treatment will be permitted.

(4) Grade 4:
- Stop the infusion and disconnect infusion tubing from subject
- Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm
- Administer diphenhydramine hydrochloride 50 mg i.v., dexamethasone 10 mg i.v. and other medications as medically necessary
- Consider hospital admission for observation
- No further treatment will be permitted.

For subjects who experience a second Grade 1 infusion reaction, administer dexamethasone 10 mg i.v. All subsequent infusions should be pre-medicated with diphenhydramine hydrochloride 50 mg i.v., dexamethasone 10 mg i.v. and acetaminophen 650 mg orally or as per institutional guidelines.

6.2.5 Dose Modifications

In both treatment arms the toxicity of each dose must be recorded prior to the administration of a subsequent dose and graded according to the NCI-CTCAE (Version 5.0). All dose reductions for all arms should be based on the worst preceding toxicity.

Prior to D1 and D15 of each new dose of treatment, the dose of drug should be determined by re-calculating the subject's BSA and it must be confirmed that subjects have haematology within the limits described in Section 6.2.3. A variation of 5% between the dose calculated by the IWRS and the total dose administered is permitted.

If a subject's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation is not permitted (with exception, see Appendix 3).

Treatment should be delayed allowing sufficient time for recovery to levels noted above, and upon recovery, treatment should be administered according to the guidelines in Appendix 2 for Arm 1 or Appendix 3 for Arm 2. The use of transfusions is permitted if within normal institutional policies and procedures (see also Section 6.3.3). If the subject had febrile neutropenia, the ANC must have resolved to 2000/mm^3 in Arm 1 and 1500/mm^3 in Arm 2; and the subject must have recovered from infection.

Dose modifications are therefore defined as the following:

- Dose reduction: the new dose should be specified.
- Infusion interruption: the timepoint, reason and timing of interruption of infusion will be recorded.
- Dose delay:
  - Arm 1: documented as such if delayed dose is given within the per-protocol maximum days permitted between doses i.e. 28 days.
  - Arms 2: documented as such if delayed dose is given within the per-protocol maximum days permitted between doses i.e. 21 days.

Any dose delays longer than the above must be discussed with the sponsor or delegate.

- Dose omission
  - Arm 1: documented as such if delayed dose >28 days i.e. more than the per-protocol maximum permitted days between doses.
  - Arm 2- documented as such if delayed dose >21 days i.e. more than the per-protocol maximum permitted days between doses.

6.2.5.1 Dose Modifications and Omissions Arm 1: Irinotecan Liposome Injection+Oxaliplatin+5-FU/LV

In Arm 1, dosing may be delayed for up to 14 days from when it was scheduled (permitting a total of 28 days between the scheduled Day 1 and Day 15 doses) to allow for recovery from toxicity related to the study treatment, administrative, or personal reasons. If the time required for recovery from toxicity is more than 14 days, the dose is marked as omitted and consideration should be given to withdrawal from treatment in the study, unless the subject is demonstrating benefit overall, in which case the possibility of remaining on study medication should be discussed between investigator and sponsor (or delegate), after review of the associated risks and benefits.

Dose level reductions required due to toxicity related to irinotecan liposome injection+oxaliplatin+5-FU/LV should be made following the guidelines outlined in Appendix 2.

Any subject who has three dose reductions and experiences an AE that would require a fourth dose reduction must be discontinued from study treatment.

If oxaliplatin is not well tolerated in subjects randomised to Arm 1, oxaliplatin may be discontinued and subjects may continue to receive irinotecan liposome injection+5-FU/LV at the discretion of the investigator and continue in the study. (For discontinuation details please see Section 4.3). In the case that oxaliplatin is removed from the regimen, the following doses and administration of irinotecan liposome injection, 5-FU/LV will occur on Days 1 and 15 of each 28-day cycle:

- Irinotecan liposome injection will be administered at 50 mg/m^2 i.v. over 90 minutes (±10 minutes)
- LV (l+d racemic form-generic form) infusion will start 30 minutes (+10 minutes) after completion of irinotecan liposome injection administration, at 400 mg/m^2, i.v. over 30 minutes (±5 minutes)
- 5-FU infusion will start within 60 minutes after completion of LV administration, at 2400 mg/m^2 i.v. over 46-hours (±120 minutes).

No dose adjustments for toxicity are required for LV.

6.2.5.2 Dose Modifications and Omissions-Arm 2: Nab-paclitaxel+Gemcitabine

Dose level reductions required due to toxicity related to nab-paclitaxel and gemcitabine should be made following the guidelines outlined in Appendix 3.

Recommended dose modifications for neutropenia and thrombocytopenia and adjustments related to other toxicities are also provided in Appendix 3.

In Arm 2 any subject who has two dose reductions and experiences an AE that would require a third dose reduction must be discontinued from study treatment (Appendix 3).

The following rules will be applied if any of the following doses are missed in the 28-day cycle for Arm 2:

- CxD1: can be delayed by a maximum of 7 days to accommodate 21 days between the previous cycle's D15 and CxD1.
- CxD8: cannot be delayed and if the subject is not well, this dose is not given, and the next dose scheduled for the CxD15 date.
- CxD15:
  - in the case that the CxD8 dose was missed, the CxD15 dose can be delayed by a further week (leading to 21 days between CxD1 and the rescheduled CxD15 dose)
  - in the case that the CxD8 dose was given on schedule, CxD15 may be delayed by a maximum of 2 weeks (leading to 21 days between CxD8 and the rescheduled CxD15 dose):

In Arm 2, the maximum delay between a missed scheduled dose and the next one (whichever dose is missed) should not be longer than 21 days to allow for recovery from toxicity related to the study treatment, and administrative, or personal reasons (see Appendix 3 for dose modification guidance). If the time required for recovery from toxicity is more than 21 days, consideration should be given to withdrawal from treatment in the study, unless the subject is demonstrating benefit overall, in which case the possibility of remaining on study medication should be discussed between investigator and sponsor (or delegate), after review of the associated risks and benefits.

*6.2.5.3 UGT1A1*28 Monitoring*

As part of this study, pharmacogenomic data will be collected on all subjects and assessed centrally for determination of the genotype at the UGT1A1 (TA)n repeat polymorphism, especially of UGT1A1*28 status. Results will be provided to the sponsor.

Based on previous experience with non-liposomal irinotecan, individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan treatment. According to the prescribing information for irinotecan [Camptosar® USPI 2016], in a study of 66 subjects who received single-agent non-liposomal irinotecan (350 mg/m^2 once every 3-weeks), the incidence of Grade 4 neutropenia in subjects homozygous for the UGT1A1*28 allele was as high as 50%, and in subjects heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%.

Importantly however, no Grade 4 neutropenia was observed in subjects homozygous for the wild-type allele (UGT1A1 6/6 genotype). Additionally, in other studies, a lower prevalence of life-threatening neutropenia has been described (for details refer to the prescribing information for irinotecan [Camptosar® USPI 2016]. Population PK studies of irinotecan liposome injection have not identified a clinically significant relationship between UGT1A1*28 homozygosity and increased SN-38 exposure (see IB). In a phase I study (UCSF 8103, as referenced in Section 2.1.1.6) no differences in toxicity were seen in cohorts of heterozygous or wild-type subjects, and dose limiting toxicities of diarrhoea with or without accompanying dehydration or fatigue, were seen in both cohorts.

All subjects treated in Arm 1, regardless of the results of the UGT1A1*28 genotype, will be treated with the same starting dose of irinotecan liposome injection and will follow the same dose reduction rules. Regular safety monitoring of subjects will be conducted by the sponsor medical monitor(s) (or delegate) and by the IDMC during the study. The safety and any available PK of UGT1A1*28 homozygous subjects will be compared to those who are non-homozygous for UGT1A1*28 to determine whether any different dosing strategy (such as a lower starting dose and/or different dose reduction for irinotecan liposome injection) is required for subjects who are homozygous for UGT1A1*28.

6.3 Concomitant Medication/Treatment/Therapy

All concurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the investigator according to acceptable local standards of medical care. Subjects should receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as necessary.

Careful monitoring of coagulation parameters is imperative, in order to avoid complications of any possible drug interactions (see below). All concomitant medications, including transfusions of blood products, will be recorded on the appropriate case report form.

Guidelines for treating certain medical conditions are discussed below; however, institutional guidelines for the treatment of these conditions may also be used. The concomitant therapies that warrant special attention are discussed below.

Any prior or concomitant therapy or medication given to a subject within 4 weeks, or within a time interval less than at least five half-lives (whichever is shorter) before study medication administration or during study medication administration will be recorded on the eCRF. Dose and generic name or trade name will be recorded.

6.3.1 Pre-Medication

6.3.1.1 Arm 1: Irinotecan Liposome Injection+Oxaliplatin+5-FU/LV

All subjects must be pre-medicated prior to irinotecan liposome injection infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics (according to

standard institutional practices). In situations where differences in standard institutional practices and recommendations within the country relevant SmPC occur, standard institutional practice will take precedence, excluding prohibited medications as per Section 6.3.2. Atropine may be prescribed as per standard of care and/or prophylactically for subjects who experienced acute cholinergic symptoms.

6.3.1.2 Arm 2: Nab-paclitaxel+Gemcitabine

Pre-medication administration is not required prior to nab-paclitaxel treatment, as hypersensitivity reactions are not expected, although initial antiemetic prophylaxis is recommended due to administration of gemcitabine following nab-paclitaxel treatment.

If a hypersensitivity reaction occurs, the infusion will be stopped and not restarted. If it is in the subject's best interests, at the investigator's discretion, treatment may continue over subsequent cycles using the pre-medication regimen that the institution typically uses for gemcitabine.

6.3.2 Prohibited Therapy and Therapy to be Monitored Closely

The following drugs are noted in the irinotecan liposome injection prescribing information as interacting with irinotecan (see Appendix 1, which lists examples of prohibited strong CYP3A, CYP2C8, and UGT1A inhibitors or inducers):

- Strong CYP3A4 inducers, e.g. St. John's Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), rifampin, rifabutin, rifapentine
- CYP3A4 inhibitors, e.g. clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole, troleandomycin, erythromycin, diltiazem, verapamil
- Strong UGT1A1 inhibitors, e.g. atazanavir, gemfibrozil, indinavir, ketoconazole.

Treatment with these agents and any others that interact with irinotecan, oxaliplatin, 5-FU, LV, nab-paclitaxel or gemcitabine should be avoided wherever possible. Aprepitant is a moderate CYP3A inhibitor and mild inducer of CYP3A4. Fosaprepitant and aprepitant interact with irinotecan: caution should be exercised when administering either agent as their use may result in increased toxicity (neutropenia and diarrhoea). For the prevention of chemotherapy-induced nausea and/or vomiting, selection of an appropriate antiemetic should avoid potential drug-drug interactions and employ a multimodal combination with either a 5-HT3 antagonist, dexamethasone, olanzapine and a NK-1 antagonist that does not interact with the CYP3A4 pathway (e.g. rolapitant). Where anti-emetic options are limited to aprepitant and fosaprepitant, these should only be used based on investigator judgement considering the risk/benefit to the subject. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. Standard institutional practices should be used for any other drug interactions.

No live attenuated vaccines should be given to subjects in the study and for 3 months after last dose of study therapy (e.g. yellow fever vaccine and polio virus vaccine). If a subject receives SARS-CoV-2 vaccinations (COVID-19 vaccinations) during study participation, it is the responsibility of the investigator to determine the suitability of the vaccine being given with the information provided by the manufacturer.

The following therapies are not permitted during the study treatment phase (see also Section 6.4 for lifestyle recommendations):

(a) Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or antibodies

(b) Potentially curative radiotherapy; palliative radiotherapy is permitted

(c) Other antiretroviral therapies with overlapping toxicities with the irinotecan liposome injection+oxaliplatin+5-FU/LV regimen, including the agent zidovudine, which has an overlapping toxicity for increased risk of neutropenia.

(d) Any other investigational therapy.

6.3.3 Permitted Concomitant Medication/Therapy

Concomitant medications for treatment of febrile neutropenia with G-CSF and diarrhoea are permitted during this study, but they must be monitored closely and every effort should be made to keep their dose and dose regimen constant throughout the course of the study.

6.3.3.1 Granulocyte Colony-Stimulating Factors

Deaths due to sepsis following severe neutropenia have been reported in patients treated with non-liposomal irinotecan and irinotecan liposome injection. In subjects with metastatic pancreatic cancer in the NAPOLI-1 study, neutropenic fever/sepsis appeared more frequently in the irinotecan liposome injection containing arms (4.8% irinotecan liposome injection monotherapy arm, 3.4% irinotecan liposome injection+5-FU/LV arm and 0.7% 5 FU/LV control arm). The incidence of Grade 3 or 4 neutropenia was higher among Asian subjects (18 of 33 (55%)) compared to white subjects (13 of 73 (18%)) (see the IB for further details).

In the ongoing phase I/II open-label, dose-expansion study of irinotecan liposome injection plus 5-FU/LV and oxaliplatin in subjects with previously untreated metastatic pancreatic cancer (MM 398-07-02-03) Grade 3 or higher treatment-related febrile neutropenia occurred in 12.5% of the pooled population treated with 50 mg/m^2 irinotecan liposome injection, LV 400 mg/m^2, 5-FU 2400 mg/m^2 and 60 mg/m^2 oxaliplatin (n=4/32) (see Section 1.2.2.1 and the IB for further details).

For both arms, neutropenic complications should be managed promptly and adequately with antibiotic support. Granulocyte-colony stimulating factor (G-CSF) may be used at the investigator's discretion for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in subjects with an ANC <500 cells/µL. Prophylactic use of G-CSF should be considered if subjects are considered high risk in the opinion of the investigator (e.g. age >60, co-morbidities, poor nutritional status, previous episode of febrile neutropenia) [Smith 2015, Klastersky 2016, Lyman 2005]. Subjects with prolonged a diarrhoeal episode lasting ≥48 hours should be closely monitored for a trend of decrease in white blood cells (WBC) and/or neutropenia with high consideration given to administer G-CSF to avoid infectious/septic complications. See Section 6.3.3.2 and the detailed algorithm of diarrhoea management for chemotherapy-induced diarrhoea provided in Appendix 5.

6.3.3.2 Therapy for Diarrhoea

Acute diarrhoea and abdominal cramps, developing during or within 24 hours after irinotecan liposome injection administration, may occur as part of a cholinergic syndrome. The syndrome can be treated with atropine. Prophylactic or therapeutic administration of atropine, according to institutional standards, should be considered in subjects experiencing cholinergic symptoms during the study.

Diarrhoea can be debilitating and on rare occasions is potentially life-threatening. Anti-diarrhoea management should be initiated at the first episode of poorly formed or loose stools or the earliest onset of bowel movements that are more frequent than normal. For both arms, diarrhoea should be managed according to institutional guidelines, or according to the guidelines developed by an American Society of Clinical Oncology panel and ESMO Clinical Practice Guidelines for treating chemotherapy-induced diarrhoea [Benson 2004, Utaris 2015, Bossi 2018].

For a detailed algorithm of diarrhoea management for chemotherapy-induced diarrhoea see Appendix 5.

6.4 Lifestyle Restrictions/Recommendations

Vacations or holidays of 14 calendar days in length can be accommodated in the schedule.

Besides restrictions already presented in the exclusion criteria (see Section 4.2) and any related to smoking or alcohol consumption, subjects will also be requested to avoid the following from 48 hours prior to Day 1 and until EoT visit:

- poppy-seeds consumption
- cannabis (including medicinal).

Subjects are to use contraception throughout the study, as well as after they stop receiving study medication, as described in Section 4.3.3.

Prior to treatment, male subjects will be informed of the possibility of irreversible infertility/testicular damage and they will be advised to consider conservation of sperm.

Subjects in Arm 1 receiving 5-FU will be advised to take measures to minimise exposure to UV light for the duration of the study and for one week after the last dose of 5-FU because of the associated risk of photosensitivity.

6.5 Procedures for Monitoring Subject Compliance

The investigator will be responsible for monitoring subject compliance. Subjects may be withdrawn from the study at any time if the investigator or the sponsor determines that the subject is not in compliance with the study protocol.

7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule in Table 5.

7.1 Primary Efficacy Endpoint and Evaluation

As described in Section 3.2.1, the primary efficacy endpoint is the OS of subjects randomised to irinotecan liposome injection+oxaliplatin+5-FU/LV compared to subjects randomised to nab-paclitaxel+gemcitabine.

7.2 Secondary Efficacy Endpoints and Evaluations

7.2.1 Time to Event Endpoints

Secondary efficacy endpoints are PFS and ORR. These are defined in Section 3.2.2. These endpoints will only be evaluated if the primary efficacy endpoint demonstrates superiority for irinotecan liposome injection+oxaliplatin+5 FU/LV over nab paclitaxel+gemcitabine. Investigator-assessed tumour response will be used in efficacy analysis.

7.3 Exploratory Efficacy Endpoints and Evaluations

The exploratory endpoints TTF, DOR and TTR are described in Sections 3.3.3, 3.3.4 and 3.3.5, respectively. These will be summarised as described in the statistical analysis plan (SAP).

The PRO exploratory endpoints are as follows:

- Assess time to deterioration or worsening of subjects physical functioning, disease related symptoms and treatment related symptoms of interest using the European Organisation for Research and Treatment of Cancer quality-of-life-core questionnaire (EORTC QLQ-C30) and, specific pancreatic cancer module (QLQ-PAN26) questionnaire and PRO of Common Terminology Criteria of Adverse Events (CTCAE)
- Assess time to deterioration or worsening on remaining QoL subscales of QLQ-C30 and QLQ-PAN26
- Compare % of subjects with stable, improved or worsened QoL scores as assessed by QLQ-C30, QLQ-PAN26 and PRO-CTCAE
- Summarise HRQoL score at each visit as assessed by QLQ-C30, QLQ-PAN26, PRO-CTCAE and EQ-5D-5L.

EORTC QLQ-C30 and QLQ-PAN26 questionnaire data will be collected to assess how subjects' functioning, disease-related symptoms and treatment-related symptoms are affected by treatment with irinotecan liposome injection+oxaliplatin+5-FU/LV in comparison with nab-paclitaxel+gemcitabine.

The EORTC QLQ-C30 is a generic questionnaire that has been developed and validated to assess the QoL of cancer patients. The QLQ-PAN26 is a disease-specific module that complements the QLQ-C30 questionnaire to capture concepts that are specific to pancreatic cancer (all disease stages) such as jaundice, digestive function, decreased muscle strength. It has not yet undergone psychometric testing in a large international group of subjects, but pre-testing has already been conducted and it is currently tested in international clinical trials. The QoL questionnaires should be completed in a language that is understood by the subject. The sponsor (or delegate) is to be consulted should a subject be illiterate or not understanding local language for advice.

Scoring will be performed as described in the EORTC QLQ-C30 scoring manual [EORTC QLQ-C30, 2001]. Scores range from 0 to 100. A high score for the global health status/QoL representing a high QoL; a high score for the functional scale representing a high/healthy level of functioning; but a high score for a symptom scale/item representing a high level of symptomatology/problems.

A subject perspective on TEAEs will be collected through the PRO-CTCAE and the EQ-5D-5L instrument will be used to provide a generic preference-based measure and health utility.

7.4 Methods and Timing of Assessing, Recording and Analysing Efficacy Data

Methods for assessing primary, secondary and exploratory efficacy data, are described in Section 3.2.1, Section 3.2.2 and Section 3.3, respectively.

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent until 30 days after the last dose of study medication (see Section 3.7 for a definition of the study duration) and will be elicited by direct, nonleading questioning. Further details for AE reporting can be found in Section 8.1.4 and 8.1.5.

Reference information for safety of study medication is listed at the beginning of Section 18.

8.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no study medication has been administered.

This definition includes events occurring from the time of the subject giving informed consent until 30 days after last study medication administration (as defined in Section 3.7).

Natural progression or deterioration of the disease under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE.

Death due to disease progression will be recorded as part of the efficacy evaluation and will not be regarded as an SAE.

Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the baseline disease.

These signs and symptoms should only be reported as AEs/SAEs (depending on the investigator's judgement) if they are:

- Judged by the investigator to be unusually severe or accelerated disease, or
- If the investigator considers the deterioration of disease signs and symptoms to be caused directly by the IMP.

If there is any uncertainty about an AE being due solely to the disease under study, it should be reported as an AE/SAE as appropriate.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

Adverse events will be recorded and graded according to NCI-CTCAE (Version 5.0). In view of meta-analyses and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

- NCI-CTCAE Grade 1 corresponds to mild,
- NCI-CTCAE Grade 2 corresponds to moderate,
- NCI-CTCAE Grade 3 corresponds to severe,
- NCI-CTCAE Grade 4 corresponds to life threatening/disabling,
- NCI-CTCAE Grade 5 corresponds to death (related to AE).

Where:

- **Mild**: symptoms do not alter the subject's normal functioning
- **Moderate**: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject

- **Severe**: symptoms definitely hazardous to wellbeing or causing significant impairment of function or incapacitation.
- **Life threatening**: any event that places the subject at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death (also see Section 8.1.5).

8.1.2.2 Causality Classification

The relationship of an AE will be assessed for each drug of the regimen for each arm and will be classified according to the following:

- **Related**: reports including good reasons and sufficient information (e.g. plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with each drug of the regimen in the sense that it is plausible, conceivable or likely.
- **Not related**: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with each drug of the regimen.

8.1.2.3 Assessment of Expectedness

The reference document for each study medication for assessing expectedness of AEs/event in this study is listed at the beginning of Section 18.

8.1.2.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in study medication schedule of administration (change in dosage, delay in administration, study medication discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are SAEs,
- They are considered as clinically significant by the investigator.

8.1.2.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the investigator, in physical examination findings (abnormalities) will be recorded as AEs.

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings judged by the investigator as clinically significant (e.g. ECG changes) that result in a change in study medication dosage or administration schedule, or in discontinuation of the study medication, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

8.1.3 Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study include:

- Thrombo-embolic events, NCI-CTCAE Grade 1 to 5

These events must be collected in the CRF using the AESI reporting option on the AE page of the eCRF. If they meet the seriousness criteria, they should also be reported as SAEs (refer to Section 8.1.5).

8.1.4 Recording and Follow-up of Adverse Events

At each visit, the subject should be asked a nonleading question such as: “How have you felt since the last visit?”

All AEs, regardless of treatment group or suspected causal relationship to study medication, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study (i.e. from signing consent up to 30 days after last study medication administration), or exacerbations of pre-existing illnesses should be recorded according to the NCI terminology if applicable. Any AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. study medication or other illness). The investigator is required to assess causality and record that assessment in the source documentation and the eCRF. Follow-up of the AE, after the date of study medication discontinuation, is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.

8.1.5 Reporting of Serious Adverse Events

All SAEs (as defined below), regardless of treatment group or suspected relationship to study medication, must be reported immediately (within 24 hours of the investigator or staff becoming aware of the event) using the SAE reporting option on the AE page of the eCRF. In case of no access to eCRF then a paper SAE form should be completed and emailed to CCI [redacted]. If the immediate report is submitted by telephone or using the paper SAE form, then this must be followed by reports using the eCRF.

An SAE is any AE that:

(1) Results in death

(2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see below)

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions

(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the study medication

(6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, it may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection should be considered serious and be immediately reported to the sponsor. The seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation).

- **Hospitalisation** is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.

- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet the criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.
- Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours of the investigator or staff becoming aware of the event), using the SAE reporting option on the AE page of the eCRF. In case of no access to eCRF then a paper SAE form should be completed and emailed to the email specified at the beginning of this protocol, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

Any AE/SAE with a suspected causal relationship to study medication administration occurring at any other time after completion of the study must be reported promptly.

The following information is the minimum that must be provided to the sponsor within 24 hours for each SAE:

- study number
- centre number
- subject number
- AE
- investigator's name and contact details.

The additional information included in the SAE page or form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

8.1.6 Pregnancy

Information regarding pregnancies must be collected as an SAE on the AE page of the eCRF and reported to the sponsor within 24 hours as described in Section 8.1.5.

If pregnancy occurs during the study, the outcome of the pregnancy will be collected following completion of the study and it may be necessary to discontinue administration of the IMP.

The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

The investigator must instruct all female subjects to inform them immediately should they become pregnant during the study. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow-up after the subject's involvement in the study has ended.

Pregnancies with a conception date within 7 months after a female subject's last dose of study medication must also be reported to the investigator for onward reporting to the sponsor.

If the investigator becomes aware of a pregnancy occurring in the partner of a male subject participating in the study, this should be reported to the sponsor as described above. Pregnancies in the partner with a conception date until 6 months after subject's last dose of study medication should be reported after the partner has given written consent and the partner should be counselled and followed as described above. Monitoring of the partner should continue until conclusion of the pregnancy.

8.1.7 Deaths

For AEs leading to death, NCI CTCAE Grade 5 is the only appropriate grade (see Section 8.1.2.1). Deaths that cannot be attributed to an NCI CTCAE term associated with Grade 5 or that cannot be reported within an NCI CTCAE category as 'Other' have to be reported as one of these four AE options:

- death not otherwise specified (NOS)
- multi-organ failure
- sudden death.

8.1.8 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the study medication (see Section 4.3).

If the study medication is discontinued due to an SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.5).

In case of suspected or confirmed COVID-19 infection, the administration of study medication may be temporarily discontinued depending on the subject clinical presentation. In some cases, the investigator may request a subject be retested before the administration of study medication is resumed. The decision to restart a subject's study treatment will be managed on an individual subject basis per the sponsor (or delegate).

In all cases, the investigator must ensure that the subject receives appropriate medical follow-up (see Section 8.1.4).

8.1.9 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The sponsor will ensure that processes are in place for the submission of reports of suspected unexpected serious adverse reactions (SUSARs) occurring during the study to the CAs, IECs and other investigators concerned by the study medication. Reporting will be in accordance with the applicable regulatory requirements.

8.2 Clinical Laboratory Tests

Full details regarding the required processing, labelling, shipment and destruction processes for these samples are provided in the laboratory manual.

Blood samples will be collected at screening, prior to each dosing visit and at the EoT follow-up visit (as per Table 5) for the evaluation of haematology and chemistry. As described in Section 6.2.3, ANC, WBC and platelets results must be obtained and reviewed prior to each dosing.

The investigator will review the safety laboratory test results, document the review and record any clinically relevant changes occurring or observed during the study in the source documentation and in the AE section of the eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the investigator and the sponsor's clinical monitor (or his/her designated representative) or until the abnormality is explained by an appropriate diagnosis.

8.2.1 Haematology

Haematology samples will be analysed at each site's local laboratory and results must be available and reviewed prior to dosing.

Blood samples will be collected to assess the following variables: haemoglobin, WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and others), platelet count and coagulation (Prothrombin Time with International Normalised Ratio and Activated Partial Thromboplastin Time).

8.2.2 Blood Biochemistry

Serum samples for blood biochemistry must be analysed centrally but can also be analysed locally in the case of requiring timely results for medical management. Centrally assessed biochemistry is required to confirm eligibility. If local laboratory results are required, the local laboratory ranges for ULN and lower limits of normal (LLN) should be included in the reporting. Central laboratory samples should always be taken, even if local laboratory samples have also been taken:

- creatinine, total bilirubin, conjugated bilirubin
- sodium, potassium, calcium, phosphate
- alkaline phosphatase, AST, ALT, gamma glutamyl transferase
- albumin, total protein.

*8.2.3 UGT1A1*28 Genotyping*

A whole blood sample will be collected and assessed centrally at baseline to test for UGT1A1(TA) repeat polymorphism, which includes UGT1A1*28 allele status. The result is not needed prior to the initial dose of irinotecan liposome injection.

8.2.4 CA19-9 Biomarker

Blood samples will be collected and assessed centrally throughout the study for the assay of CA19-9 biomarker levels. The CA19-9 biomarker levels will be collected for all subjects as per Table 5.

8.2.5 Pregnancy Test

A urine or beta human chorionic gonadotrophin (HCG) serum test will be performed locally for all female subjects of childbearing potential as per Table 5. Any positive urine pregnancy test must be confirmed via serum β-HCG. Exempt female subjects will include those who have undergone a bilateral oophorectomy, bilateral salpingectomy or hysterectomy or who are menopausal (defined as absence of a menstrual cycle for at least 2 years). Any subject becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.6.

8.2.6 Urinalysis

Urinalysis (dipstick) will be completed locally and undertaken as per schedule of assessments in Table 5.

8.2.7 Dihydropyrimidine Dehydrogenase Testing

Dihydropyrimidine dehydrogenase (DPD) testing, where required by local regulations, will be undertaken as per schedule of assessments in Table 5 and as detailed in Appendix 7. Results

should be received and reviewed prior to randomisation to ensure patients with low or absent DPD activity will not be enrolled in this study.

8.3 Physical Examination

Physical examinations, including neurological examination will be conducted as per schedule of assessments in Table 5.

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.4 Vital Signs

Vital signs will include height (at screening only) weight, resting blood pressure, pulse and temperature. BSA is calculated within 2 days before D1 and D15 of each cycle before treatment administration.

8.5 Electrocardiography

The ECGs will be recorded at the timepoints described in Table 5, including footnotes specifying the different requirements for Arm 1 and Arm 2.

Any clinically significant abnormalities will be recorded as AEs.

A 12-lead ECG will include a description of the cardiac rate, rhythm, interval durations and an overall clinical interpretation. If the ECG is abnormal, clinical significance or non-significance should be indicated. Any QTc prolongation that occurs in the setting of diarrhoea induced electrolyte imbalance should be treated with appropriate electrolyte repletion. Once the underlying abnormality is corrected and the ECG abnormalities have reversed, treatment may continue under careful monitoring and with appropriate dose modification for diarrhoea as described in Appendices 2 and 3.

8.6 Performance Status

The ECOG performance status will be recorded at the timepoints in Table 5. The ECOG will be assessed by the investigator or his/her designee via questioning of the subject about their functional capabilities. See Appendix 6 for ECOG.

9 ASSESSMENTS OF PHARMACOKINETICS

9.1 Pharmacokinetics

9.1.1 Sample Collection

For subjects in Arm 1, blood samples for the determination of total irinotecan, SN-38, 5-FU and oxaliplatin plasma concentrations will be collected at the timepoints indicated in Table 7. Additional analytes which may impact the PK of irinotecan liposome injection may also be measured from this sample.

During the study, the nominal sample collection times may be changed, but the total number of samples will not increase. The exact dates and times of blood sample collection, study medication administration must be recorded in the eCRF.

Directions for collection, processing and shipping the PK plasma samples can be found in the laboratory manual. Full details regarding the destruction processes for these samples are documented in the PK Sample Management Plan.

The number of draws (and consequently the number of aliquots collected) are detailed in Table 7.

Irinotecan and SN-38 levels will be measured in a same aliquot. 5-FU and oxaliplatin levels will be measured in different aliquots.

- Sample 1: three aliquots will be collected for irinotecan and SN-38, 5-FU, oxaliplatin determination
- Sample 2: one aliquot will be collected for irinotecan and SN-38 determination
- Sample 3: two aliquots will be collected for irinotecan and SN-38, oxaliplatin determination
- Sample 4: three aliquots will be collected for irinotecan and SN-38, 5-FU, oxaliplatin determination
- Sample 5: two aliquots will be collected for irinotecan and SN-38, oxaliplatin determination
- Sample 6: two aliquots will be collected for irinotecan and SN-38, oxaliplatin determination.

Table 7 Summary of Pharmacokinetic Sampling Timepoints

Sample	Time-point	Number of Draws	Window
1	Cycle 1 Day 1 (Pre-Dose): prior to irinotecan liposome injection infusion	3	-24 hours
2	Cycle 1 Day 1: at the end of the irinotecan liposome injection infusion	1	+15 mins
3	Cycle 1 Day 1: at the end of the oxaliplatin infusion	2	+5 mins
4	Cycle 1 Day 3: within 2 hours prior to the completion of the 5-FU infusion	3	-
5	Cycle 1 Days 4 to 14 (Optional[a]): anytime between 1 and 11 days after the end of the 5-FU infusion	2	N/A
6	Cycle 1 Day 15 (Pre-Dose): prior to irinotecan liposome injection infusion	2	-24 hours

5-FU=5-fluorouracil, N/A=not applicable

a Optional sampling: to be taken if the subject visits or is at the clinic on these days.

9.1.2 Analytical Procedures

Plasma samples will be analysed to determine concentrations of total irinotecan, SN-38, 5-FU and oxaliplatin using validated, specific and sensitive liquid chromatography-mass spectrometry methods.

9.1.3 Use of Samples After Study Completion

Leftover samples (plasma) may be used, during the course of the study, or after completion of the study to develop new laboratory tests (such as sample stability assessment, analytical comedication interference or cross-validation of the bioanalytical method or other bioanalytical assessments such as additional analytes that may impact the pharmacokinetics of the drug). If the subject consents to this, the samples will be stored up to 1 year after the end of the study in a bioanalytical contracted research organisation (CRO) contracted by the sponsor. Subjects will be informed that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10 EXPLORATORY BIOMARKERS AND BIOBANKING

Biobanking sample collection is optional, requiring separate optional informed consent from participants (see Section 14.2.1). Samples for biobanking will be collected as follows:

- Archived tumour samples at baseline, if available
- Whole blood for DNA (2.5 mL)
- Whole blood for RNA (2.5 mL)
- Whole blood for plasma (4 mL)
- Stool sample
- Whole blood for circulating free DNA (10 mL).

An additional 16.5 to 19 mL of blood will be collected from subjects who have signed the optional biobanking informed consent. This will be taken prior to treatment dosing, for a total of 19 mL at Cycle 1 Day 1 and 16.5 mL at Day 1 of every other cycle (C3D1, C5D1, C7D1 etc). Whole blood (for DNA, RNA, circulating free DNA and plasma) and stool samples will be collected as follows in both Arm 1 and Arm 2:

- At baseline (Cycle 1 Day 1) prior to treatment dosing: whole blood samples (for DNA, RNA, circulating free DNA and plasma) and stool sample.
- At Day 1 of every other additional cycle (i.e. C3D1, C5D1, etc) prior to treatment dosing: whole blood samples (for RNA, circulating free DNA and plasma) and stool sample.

Instructions for collection, processing, handling and shipment of the biobanking samples will be outlined in the laboratory manual. Full details regarding the destruction processes for these samples are documented in the Biobanking Sample Management Plan.

CCI [redacted]

The biobanked samples will be stored for up to 15 years from the end of the study to be made available for future research towards further understanding of:

(1) treatment response including, but not limited to, the safety profile

(2) drug treatment mode of actions, and

(3) disease understanding.

Samples will be archived in a central biorepository designated by the sponsor and according to local administration regulations and/or the EMA and will not carry personal identification (e.g. social security number or name). Analysis of additional biomarkers (including potential genetic research) from the biobank samples will be performed outside the scope of the main study and reported separately.

Only people designated by the sponsor will be allowed access to the samples. All information collected will be kept strictly confidential and all clinical information will be de-identified. This means that no personally identifiable information will be retained with the results of the exploratory analyses, so that no individual or collective results will be linked to the individual subject whose sample was taken in the study. No individual genetic results will be communicated to the investigator or subject unless required by local regulation.

The sponsor will comply with all local regulations related to the establishment, management and application of a human blood samples biobank.

11 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the SAP, which will be dated and completed before first subject being randomised. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (Version 9.3 or higher)

11.1 Analysis Populations

The following populations will be used during statistical analyses:

- **Screened population**: All subjects screened (i.e. who signed the informed consent).
- **Intention-to-Treat (ITT) population**: This population includes all randomised subjects who have given their informed consent. A subject is randomised (after informed consent has been provided) if there is confirmation of successful allocation of a randomisation number through the study treatment allocation system (IWRS). This population is the primary population for all efficacy parameters. All analyses using this population will be based on the treatment assigned by IWRS.
- **Safety population:** The safety population is a subset of the ITT population that received at least one dose (including a partial dose) of any study medication. This population is for safety analyses. All analyses using this population will be based on the treatment actually received.
- **Per protocol (PP) population**: This is a subset of the ITT population. It includes subjects who have no major protocol deviations (i.e. that could potentially affect the primary efficacy analysis for the subject) as described in the protocol deviations document. Subjects will be analysed as randomised.
- **PRO population:** All subjects of the randomised ITT population that have provided baseline and at least one subsequent assessment on each PRO instrument.
- **Pharmacokinetics population**: All subjects who received at least one irinotecan liposome injection and who have at least one plasma concentration and no major protocol deviations affecting PK variables.

11.1.1 Populations Analysed

The final analysis based on the primary efficacy endpoint will be performed on the ITT population. In addition, PP analysis may be performed as secondary/confirmatory.

The analyses of safety data will be performed based on the safety population.

11.1.2 Reasons for Exclusion from the Analyses

Any major protocol deviation (see Section 13.1.2 for definition) will be described and its impact on inclusion in each analysis population (ITT, PP and safety populations) for any subject will be specified. The final list of protocol deviations impacting the safety, ITT and PP populations will be reviewed prior to database lock. The list may be updated, up to the point of database lock, to include any additional major protocol deviations impacting inclusion in the PP population.

11.2 Sample Size Determination

The primary objective of this study is to compare OS in subjects treated with irinotecan liposome injection+oxaliplatin+5-FU/LV to OS in subjects treated with nab-paclitaxel+gemcitabine.

Approximately 750 subjects will be randomised in a 1:1 ratio to the two treatment arms. Accounting for the planned interim analysis, follow-up until at least 543 OS events are observed across the two treatment arms provides at least 90% power to detect a true HR ≤0.75 (modified OS: 9 versus 12 months) using a stratified log rank test with overall 1-sided significance level of 0.025 (adjusted for interim analysis). The study plans to enrol 750 subjects, with expected follow-up time for the final analysis at 15 months from the last subject enrolled to the 543rd OS event. For operational purposes, the expected timing of the final analysis triggering event will be periodically projected using blinded study data regardless of treatment arm. The sample size may be increased if a review of the accumulating OS events suggests that the timing of the final analysis will be extended. If blinded projection of the accumulating OS events suggests that the number required for the final analysis will not be reached (due to censoring) within 32 months of study initiation, the sample size may be increased up to 800 subjects or until prespecified events are met, whichever comes earlier. The projection to inform the decision to potentially increase the number of subjects will be carried out within 3 months prior to expected completion of planned enrolment of 750 subjects.

Assuming enrolment over 16 months increasing to approximately 62 subjects per month and lost-to-follow-up rate of 5% across both treatment arms, the timing of the interim analysis is expected to be at 24 months after the first subject treated and the timing of the final analysis, estimated via simulation, is expected to be at 36.5 months after the first subject treated.

11.3 Significance Testing and Estimations

The evaluation of the primary endpoint OS includes an interim analysis for futility and efficacy, and a final analysis with a prospective error-spending plan to control the overall type I error rate at a one-sided 0.025 level and overall type II error rate at 0.100 level. The interim analysis is planned when at least 272 OS events (i.e. 50% of information time) have been observed in the ITT population. If the OS analysis does not indicate futility at interim analysis, the final analysis is planned when 543 OS events are observed.

An alpha and beta spending function according to Hwang-Shi-Decani (HSD) γalpha=-4 and γbeta=-1 will be utilised to control type I and type II error for the OS comparison. In the computation of the type I error rate, futility analyses are considered non-binding. Since the futility and efficacy boundary is dependent on the number of OS events, the actual boundary used will be re-calculated, incorporating the spending function as defined, based on the number of actual OS events analysed at the time of analysis. P-boundary will be used as the criteria for the formal statistical inference.

The interim analysis specifications per the plan are provided in Table 8.

Table 8 Type I (α) and Type II (β) Error Spending for the Planned Analyses

(α = 0.025)

		Futility				Efficacy			
Analysis	**D**	**$Z_{boundary}$**	**$p_{boundary}$**	**CUM β spend**	**HR_{crit}**	**$Z_{boundary}$**	**$p_{boundary}$**	**CUM α spend**	**HR_{crit}**
Interim	272	-0.592	0.277	0.038	0.931	-2.750	0.003	0.003	0.716
Final	543	-1.981	0.024	0.100	0.844	-1.981	0.024	0.025	0.844

D = # of OS events at analysis. Z-boundary is the critical test statistic value at which futility (< Z) or efficacy (> Z) would be concluded. P-boundary is the critical one-sided p-value threshold for the comparison. Cum α-spend and cum β-spend are the amount of cumulative type I and type II error spent at each analysis, respectively. HR_{crit} is the observed hazard ratio threshold (> HR for futility, < HR for efficacy).

Secondary efficacy endpoints (PFS and ORR) will only be evaluated if the primary efficacy endpoint demonstrates superiority for irinotecan liposome injection+oxaliplatin+5-FU/LV over

nab-paclitaxel+gemcitabine. Investigator-assessed tumour response will be used in secondary efficacy analyses. If the primary endpoint of OS is declared significant at the interim, secondary endpoints will be tested at the interim. Otherwise, secondary efficacy endpoints will be tested at the final analysis if OS is found to be statistically significant at that analysis. Hypothesis testing of secondary endpoints will be conducted in a stagewise hierarchical manner incorporating alpha spending for each endpoint using HSD γ_{alpha}= -4, similar to that specified for the primary efficacy analysis. The nominal level for each comparison will depend on whether the analysis is carried out at the interim or at the planned final analysis.

The first endpoint in the hierarchy of secondary endpoints will be PFS. If OS and PFS are both significant, then ORR would be tested. Any parameter which is not formally tested for significance (per the hierarchy) will be regarded as descriptive and exploratory.

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's biometry department. All planned efficacy and safety analyses will be done using SAS®.

Categorical variables will be summarised by frequency distributions (number and percentage of subjects). Continuous variables may be summarised by a clinically relevant discretisation of the variable.

All CIs for parameters to be estimated will be constructed with a significance level α =0.05 (i.e. a 95% CI). Additional exploratory analyses may be conducted as deemed appropriate.

The interpretation of study results will be the responsibility of a sponsor physician and statistician. The sponsor's physician and statistician will also be responsible for the appropriate conduct of an internal review process for both the final study report and any study related material to be authorised by the sponsor for publication.

11.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data will be presented by treatment group on the ITT population. No formal statistical analysis will be performed on these data.

Subject characteristics will be summarised and compared between study treatment arms.

This will include a comparison on:

- Subject demographics
- Baseline disease characteristics
- Baseline disease-related symptoms
- Pre-existing conditions
- Prior and concomitant drugs ongoing at baseline.

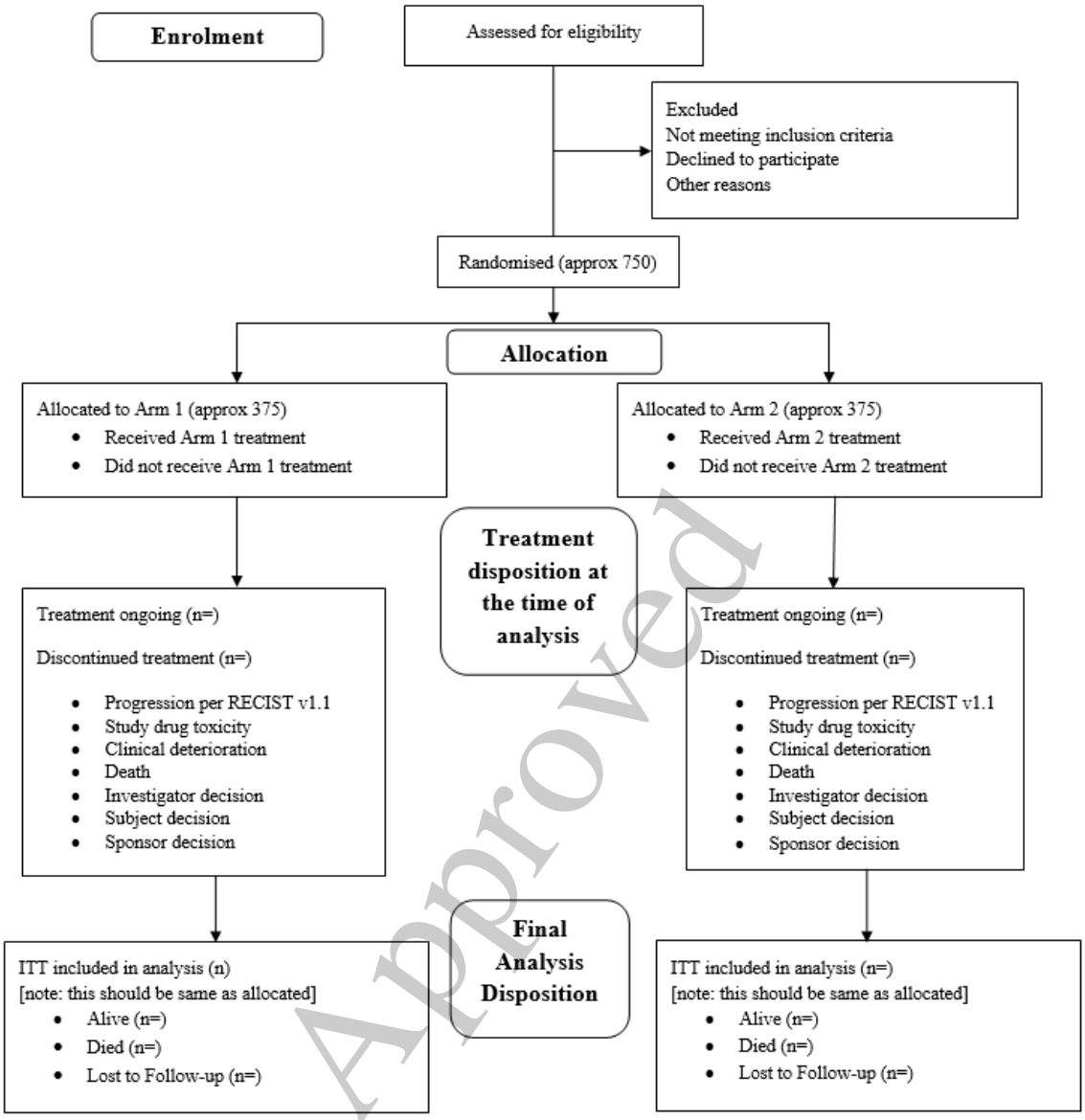
Additional subject characteristics may be summarised and compared between Arm 1 and Arm 2 as deemed appropriate.

Unless prohibited by local regulation, race and ethnicity will be collected to ensure data robustness for safety and efficacy evaluation and to prevent adverse reactions or improve benefits in the target population.

11.4.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in each of the ITT and safety populations will be tabulated. In addition, the numbers of subjects who were randomised, treated, discontinued and completed at each of the study periods will be tabulated by treatment group. Primary reasons for discontinuation of study treatment will be tabulated.

Figure 3 CONSORT Flow Diagram



11.4.3 Pharmacokinetic Data

11.4.3.1 Listings and Summary Statistics of Concentrations

Individual plasma concentrations for total irinotecan, SN-38, 5-FU and oxaliplatin will be listed and summarised by timepoint and dose level using descriptive statistics for continuous variables (number of available observations, mean, median, SD, minimum, maximum, geometric mean and geometric coefficient of variation assuming log-normally distributed data).

Linear and semilogarithmic plots of individual and mean plasma concentration-time profiles of irinotecan and SN-38 as well as spaghetti plots will be reported.

11.4.3.2 Pharmacokinetic Data Analysis

Plasma concentrations of total irinotecan and SN-38 will be used to characterise their corresponding PK parameters, in co-administration with 5-FU and oxaliplatin, using a nonlinear mixed effects approach. If warranted by the data, parameters reported after single dose could include, but not be limited to:

- Maximum observed plasma drug concentration (C_{max})
- Concentration at the end of the dosing interval (C_{trough})
- Time to maximum observed plasma drug concentration (t_{max})
- Area Under the plasma concentration‑time curve over the dosing interval (AUC_{Tau})

If warranted by the data, plasma concentrations for 5-FU and/or oxaliplatin will be used to calculate individual PK parameters after single dose. These may include, but not be limited to:

- Total clearance of drug from plasma
- Area Under the plasma concentration‑time curve over the dosing interval (AUC_{Tau})

A full description of the analysis of the concentration data will be captured separately in a data analysis plan, and PK results will be reported in a standalone report.

11.4.3.3 Pharmacokinetics/Pharmacodynamics Relationship

Graphical exploration will be performed to investigate any relationship between PK and pharmacodynamic endpoints (efficacy, safety). If a trend is shown, PK/PD modelling will be performed and this will be described in a separate Data Analysis Plan and reported in a standalone report.

11.4.4 Efficacy Evaluation

11.4.4.1 Primary Efficacy Analysis

The primary endpoint of this study is OS, which is defined as the time from the date of subject randomisation to date of death or the date last known alive. For each subject who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data cut-off date.

The OS for each treatment arm will be summarised by median survival time (including 95% CIs) from Kaplan-Meier estimation. The Kaplan Meier curve for survival will be presented for each treatment arm. Stratified analyses based on the randomisation stratification factors from the IWRS data will be used in all stratified analyses for treatment comparisons on the ITT population. Differences in the OS curves will be tested using a stratified log-rank test. The estimated treatment effect for Arm 1 will be summarised by the HR (including 95% CI) from stratified Cox regression analysis.

The following additional sensitivity analyses may be carried out for OS on the ITT population and/or PP population to evaluate the robustness of the final analysis results:

- log-rank comparisons of treatments on the PP population
- Wilcoxon comparisons of treatments on the ITT population and PP population
- log-rank test comparisons of treatments with OS censored at the date where any post-treatment anti-cancer therapy is first administered on the ITT population
- Cox regression model with stepwise selection (p value to enter <0.25, p-value to remain <0.15) of model terms where treatment and the prognostic factors (noted below) are candidates for inclusion
- univariate analyses to evaluate potential independent prognostic factors using Cox regression.

Subgroup analyses will also be performed to examine differences in the effects of treatment in different segments of the study population.

Prognostic factors to be examined may include: baseline ECOG, baseline albumin, ethnicity, geographic location, disease stage at diagnosis, original tumour location, prior radiotherapy, prior surgery, time since last treatment, best response on prior treatment, baseline CA 19-9, gender and age.

11.4.4.2 Secondary Efficacy Analysis

The secondary efficacy endpoints (PFS and ORR) will only be evaluated if the primary efficacy endpoint demonstrates superiority for irinotecan liposome injection+oxaliplatin+5-FU/LV over nab-paclitaxel+gemcitabine. Investigator-assessed tumour response will be used in the secondary efficacy analyses.

The PFS is defined as time from the date of randomisation to the date of death or progression, whichever occurred earlier (per RECIST Version 1.1). If neither death nor progression is observed, data will be censored on the date of the last evaluable tumour assessment.

General censoring rules for the analysis of PFS are described below:

- Subjects who receive non-protocol therapy before a PFS event (documented progression or death) will be right censored at the date of the last evaluable tumour assessment prior to the date of initiation of subsequent therapy/surgery
- Subjects who have not experienced a PFS event (and are not otherwise censored) at the time of data cut-off will be right censored on the date of their last evaluable tumour assessment post randomisation that is on or prior to the data cut-off. If there is no such tumour assessment post randomisation, the subject will be right censored on the date of randomisation
- Subjects who miss two or more scheduled tumour assessments followed by a PFS event will be right censored on the date of their most-recent tumour assessment prior to the missing assessments.

Detailed censoring rules and sensitivity analyses will be specified in the SAP.

For each arm, PFS will be estimated by Kaplan-Meier methodology. Treatment arms will be compared for PFS using stratified log-rank test and the estimated HR from stratified Cox regression analysis will be presented to summarise the effect of Arm 1. Estimates of median PFS and HR will be presented with corresponding 95% CIs. In addition, different censoring and missing data imputing methods may be used to perform sensitivity analyses on PFS. Methodology for the sensitivity analyses will be fully specified in the SAP.

Analysis of PFS will be performed for ITT and PP populations.

The ORR is defined as the proportion of subjects with a BOR of confirmed complete response or partial response per RECIST Version 1.1. BOR is defined as the best response as recorded from randomisation until documented objective disease progression using RECIST Version 1.1. To classify BOR as stable disease, there should be a qualifying stable disease assessment at least 8 weeks from randomisation.

The ORR of irinotecan liposome injection+oxaliplatin+5-FU/LV arm will be compared to the nab-paclitaxel+gemcitabine arm. Differences in ORR between Arm 1 and Arm 2 will be provided with 95% CIs. A Cochran-Mantel-Haenszel test, adjusting by randomisation strata, will be used to compare ORR. Analysis of ORR will be performed for ITT and PP populations.

11.4.4.3 Patient-Reported Outcomes Analysis

The PRO exploratory endpoints are described in Section 7.3.

Analyses of quality of life is an exploratory analysis that will be carried out on treated subjects who provide baseline and at least one post-baseline assessment (i.e. there will be instrument-specific analysis populations). EORTC QLQ-C30, QLQ-PAN26, EQ-5D-5L and PRO-CTCAE results will be summarised at each visit by treatment group. More details of the PRO analyses will be provided in the SAP.

11.4.5 Safety Evaluation

The safety endpoints are indicated in Section 3.2.3.

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population.

All AEs will be coded according to MedDRA Version 22.0 or later and will be classified by MedDRA preferred term and system organ class. Adverse event listings will be presented by subject, system organ class and preferred term.

The incidence of all reported TEAE and SAEs will be tabulated by arm and overall. In addition, summary tables will be presented by maximum severity (per NCI-CTCAE) drug relationship and TEAEs associated with premature discontinuation of study treatment. All the safety data will be described by grade (all grades and Grade 3 and higher).

A TEAE is defined as any AE that occurs during the active phase of the study (between first dose of study medication and 30 days after the end of study treatment) if:

- it was not present prior to receiving the first dose of study medication, or
- it was present prior to receiving the first dose of study medication but the grade increased or became serious during the active phase of the study, or
- it was present prior to receiving the first dose of study medication, the grade/seriousness is the same but the causality changed to "related" during the active phase of the study.

All TEAEs will be flagged in the AEs listings.

Summary statistics (mean, median, SD and range as appropriate) will be presented by treatment group and overall for vital signs, blood pressure, heart rate, ECG variables, clinical laboratory tests etc. at each assessment, with change from baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented for the number and percentage of subjects with low, normal or high values and normal or abnormal examinations.

The AEs reported by investigators using the NCI-CTCAE classification (Version 5.0) will be coded using MedDRA (Version 22.0 or later).

Summary incidence tables will be provided by treatment arm, classified by body system, preferred term and associated NCI-CTCAE worst grade. In the event of multiple occurrences of the same AEs being reported by the same subject, the maximum intensity (Grade 5 >Grade 4 >Grade 3 >Grade 2 >Grade 1 >missing >not applicable) will be chosen. Dose delays, omissions, and infusion interruptions will be listed by cycle. Summaries of events that resulted in dose modifications (e.g. delay, reduction) will also be provided.

Haematological and biochemical toxicities will be recorded and graded according to the NCI-CTCAE criteria, where available. The NCI-CTCAE Grade 3 and 4 haematology and biochemistry variables by subject and by cycle will be listed.

11.5 Subgroup Analyses

Descriptive statistics for primary and key secondary endpoints may be provided within each category of the following variables:

- presence of liver metastases at baseline
- number of metastatic sites
- baseline ECOG performance status (0/1)
- region (North America/East Asia/Rest of the World)
- disease stage at diagnosis
- primary tumour location

- baseline CA 19-9
- race
- gender
- age (<65 years, ≥65years, >75 years).
- UGT1A1*28 allele status (homozygous/other).

Other subgroups will be defined in the Statistical Analysis Plan (SAP).

11.6 Independent Data Monitoring Board and Interim Analysis

An IDMC will be established for this study to operate as an independent expert advisory group with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals. As such, the primary objective of the IDMC is to monitor the safety of the subjects enrolled in the study by reviewing the available clinical data at scheduled time points, to be described in the IDMC Charter, as well as on an ad hoc basis, as needed. Items reviewed will include (but not limited to) safety events, any available results of PK testing, and UGT1A1*28 genotype. Attention will be paid to determining whether any study procedure needs to be modified for subjects who are homozygous for the UGT1A1*28 allele.

The same IDMC will evaluate also the efficacy data as well as the safety data at the time of the interim analysis. The IDMC will be responsible for reviewing the futility and efficacy results in the interim analysis and making appropriate recommendations based on those results.

The operating procedures of the IDMC will be based on and in compliance with the FDA's "Guidance for Clinical Trial Sponsors [on the] Establishment and Operation of Clinical Trial Data Monitoring Committees" (March 2006, OMB Control Number: 0910-0581) and with the EMA's "Guideline on Data Monitoring Committees" (January 2006, EMEA/CHMP/EWP/5872/03 Corr).

The planned frequency of the IDMC is planned to be as follows and will be agreed with the IDMC experts:

- After the 50th randomised subject has been followed for at least 28 days (follow-up time-frame equivalent of one cycle)
- Every 6 months and additionally timed with the planned interim analysis:
  - Interim analysis for futility and efficacy (no less than 50% of the planned final number of OS events in ITT population i.e. 272 of 543)

All the details of IDMC activities will be described in the IDMC charter.

12 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external Regulatory Authorities and sponsor authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 13.4 and to any other locations used for the purpose of the study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor's representative as soon as possible, to assist with preparations for the inspection.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Protocol Amendments and Protocol Deviations

13.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration.

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- ***Non-substantial amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs or regulatory authorities for information purposes.
- ***Substantial amendments*** are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the subjects;
  - the scientific value of the study;
  - the conduct or management of the study; or
  - the quality or safety of the study medication used in the study.

  Substantial amendments must be submitted to and approved by the IECs and relevant regulatory authorities, according to local regulations, prior to implementing changes.
- ***Urgent amendments*** are those that require urgent safety measures to protect the study subjects from immediate hazard and as such may be implemented immediately by the sponsor with subsequent IECs and regulatory authority notification, forthwith.

The principal investigator and the sponsor will sign all protocol amendments.

13.1.2 Protocol Deviations and Exceptions

All protocol deviations will be identified and recorded by the sponsor or sponsor's representative.

A major protocol deviation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria and/or GCP guidelines. Generally, a protocol deviation qualifies as major if:

(1) The deviation has harmed or posed a significant or substantive risk of harm to the research subject

(2) The deviation compromises the scientific integrity of the data collected for the study

(3) The deviation is a wilful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s)

(4) The deviation involves a serious or continuing noncompliance with any applicable human subject protection regulations, policies, or procedures

(5) The deviation is inconsistent with the sponsor's research, medical and/or ethical principles.

See also Section 11.1.2 for details on the impact of major protocol deviations on the inclusion of subjects in each analysis population.

As a matter of policy, the sponsor will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If investigative centre personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must

immediately inform the sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP. Retention of these subjects in the study will be discussed between sponsor and investigator, taking into account subject safety and data reliability. The IRB/IEC will be informed if subject safety/protection is ignorantly impacted.

13.2 Information to Study Personnel

To ensure accurate, complete and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A study initiation visit will be conducted prior to screening start to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRF and all study procedures. The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities. These study staff members must be listed on the study centre log, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

13.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring these data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP guidelines and regulatory requirements.

Sponsor assigned monitors will conduct regular site and/or remote visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF and will assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name (or other identifiable details) is revealed on a document required by the sponsor (e.g. laboratory print outs) the information must be blacked out permanently by the site personnel and the document annotated with the subject number as identification.

13.4 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP guidelines. This includes that the study may be audited at any time by a quality assurance personnel designated by the sponsor or inspected by regulatory bodies. The investigator must adhere to ICH GCP guidelines in addition to any applicable local regulations.

If requested, the investigator will provide the sponsor, applicable regulatory agencies and applicable EC with direct access to any original source documents.

The investigator(s) should demonstrate due diligence in recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the sponsor. The sponsor should be notified of any projected delays, which may impact the completion of the study.

This clinical trial will be conducted in compliance with all international laws and regulations and national laws and regulations of the country(ies) in which the clinical trial is performed, as well as any applicable guidelines.

13.5 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 12).

13.6 Data Quality Assurance

All eCRFs completed by the investigational site will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

14 ETHICS

14.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP guidelines (Section 1.6).

For EDC studies the following regulations are adhered to: FDA 21 CFR Part 11, Electronic Records, Electronic Signatures and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, this study will adhere to all local regulatory requirements.

Before initiating the study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written ICF, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

14.2 Informed Consent for Participation in the Study

Prior to study entry, the investigator, or (if applicable under local regulatory guidelines) a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the study medication). Sufficient time will be allowed to discuss any questions raised by the subject.

As applicable under local regulatory guidelines, the sponsor will provide a sample ICF. The final version controlled form must be agreed to by the sponsor and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed ICF.

The ICF may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study are informed of these changes and sign the amended form. This is documented in the same way as described above. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

14.2.1 Optional Informed Consent for Biobanking

This study has the option for subjects to consent to the collection of samples for biobanking for future exploratory analysis and storage for up to 15 years (where local regulations allow). A

specific informed consent is required for the collection of these samples and will be explained after the subject has given written informed consent for the main study.

Subjects must receive an explanation that they are completely free to refuse to enter the exploratory part of the study and may withdraw from it at any time and for any reason up to 15 years after the end of the study and will still be allowed to take part in the main study.

14.3 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol required services are being paid directly or indirectly.

Financial disclosure statements will be completed, as requested by FDA 21 CFR Part 54.

14.4 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the sponsor's Regulatory Affairs group (or delegate CRO) will ensure all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

The following documents should be submitted to the relevant ethics committee(s) (EC) for review and approval to conduct the study (this list may not be exhaustive and is dependent on country requirements):

- protocol/amendment(s) approved by the sponsor;
- currently applicable IB or package labelling;
- relevant investigator's curriculum vitae;
- subject information and informed consent document(s) and form(s);
- subject emergency study contact cards;
- recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required and a written favourable opinion for the conduct of the study should be made available to the investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the investigative site(s) only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC, either for information, or for review and approval, depending on how substantial the modifications are: (1) IB; (2) reports or listings of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the EC will be notified about the study completion.

14.5 Confidentiality Regarding Study Subjects

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other

documents or image material submitted to the sponsor, subjects will be identified by an identification code and not by their names, initials or date of birth.

Personal medical information may be reviewed for the purpose of verifying data recorded on the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

15 DATA HANDLING AND RECORD KEEPING

15.1 Recording of Study Data

In compliance with GCP guidelines, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

The investigator must record all data relating to protocol procedures, study medication administration, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF. Subjects' questionnaires will be collected using an electronic patient-reported outcome (ePRO) system.

The investigator (or delegated sub-investigator) must provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF after a form has been locked and electronically signed, the investigator (or delegated sub-investigator) will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF and ePRO system will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

15.2 Data Management

Electronic data capture will be utilised for collecting subject data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be made under the e-signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO, directed by the sponsor's Biometry department. All data management procedures will be completed in accordance with the contracted CRO SOPs.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history, surgical procedures and concomitant medication terms will be performed by the sponsor's central coding group and reviewed and approved by the sponsor. Concomitant medications will be coded using WHODRUG and AEs/medical history terms will be coded using MedDRA (Version 22.0 or later).

Only data from screened subjects will be reported in the eCRFs and collected in the sponsor's database.

For screen failure subjects, only the Unique Subject Identifier, the date of informed consent signature, the reason why the subject failed screening and the potential AEs which occurred

during the screening phase will be reported in the eCRFs and collected in the sponsor's database.

15.3 Record Archiving and Retention

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study 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. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

15.4 Use of Data After Study Completion

The study data from consenting subjects may be used, after the end of the study, outside the strict context of this study for further or complementary analysis, to better understand the study disease or related conditions. The data will be retained while related research activities continue but no longer than 25 years after study completion or other period as per local requirements. Each subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law and will be informed that they are free to refuse. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

16 FINANCING AND INSURANCE

16.1 Insurance, Indemnity and Compensation

The sponsor will provide product liability insurance for all subjects included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

17 REPORTING AND PUBLICATION OF RESULTS

17.1 Publication Policy

The sponsor is committed to disclosing information about the clinical trials it sponsors. Results will be communicated at scientific meetings and all reasonable efforts must be made to seek publication in a peer-reviewed scientific journal. Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate Global Publications Manager and incorporated in the relevant publication plan before initiation. A dedicated Publications Committee, involving interested members of the study Steering Committee as well as the Global Publications Manager, may be established to plan specific publications. As a minimum, summary results of this study should be posted on the relevant clinical trial registry. When the trial has been conducted by a large multicentre group, the principal investigator, the study steering committee (if applicable) and the sponsor's responsible physician should discuss and agree the selection of authors for planned publications in advance. They may decide to use a group name and nominate authors on behalf of the study group. All contributing investigators will be listed in the acknowledgements together with any others who may have contributed but not sufficiently to qualify for authorship.

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines [http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html]. In particular, those named as authors, whether employed by a sponsor's affiliate or the sponsor, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Each author must agree to their inclusion in the list of authors. Use of professional medical writing support may be employed.

Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

The sponsor requests acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor. Any medical writing support should also be acknowledged.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study

All publications arising from this study will be reviewed by relevant functions at the sponsor, coordinated by the Global Publications team. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along

principles of honest scientific debate. The sponsor's review comments must be answered before a final version for submission can be approved by the author team.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

17.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. A final CSR will be prepared where any subject has signed informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate, an abbreviated report may be prepared. The CSR will comply with any applicable regulatory requirements, national laws in force and will be in English.

As indicated in Section 11.2, an analysis will be performed on the final OS data after the last subject has completed the treatment period. This analysis will be included in the final study report. Should any subjects remain on treatment at the time of the final analysis an addendum to the report will be prepared after the last subject completes study treatment.

Analysis of biobank samples will be performed outside the scope of the main study and reported separately.

18 REFERENCES

Reference Documents for study medication for safety information:

- Irinotecan liposome injection: Investigator's Brochure

Reference Documents as per electronic medicines compendium (emc) https://www.medicines.org.uk/emc

- Oxaliplatin SmPC
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- LV SmPC
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- Gemcitabine SmPC

Note: where applicable, local prescribing information should be used.

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Appendix 1 Concomitant Use of Enzyme Inducers and Inhibitors

The use of strong CYP3A, CYP2C8, and UGT1A inhibitors or inducers are not allowed during the study and specific moderate CYP3A inhibitors and mild inducers of CYP3A4 should be approached with caution, as detailed below. Specific stopping periods prior to randomisation for enzyme inhibitors and inducers are described below. CYP3A/2C* and UGT1A enzyme inhibitors and inducers include prescribed medicines, over the counter medicines, complementary and alternative medicines, food supplements and food substances.

Examples of strong inducers and inhibitors

- Strong CYP3A inducers: rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John's wort, avasimibe, lumacaftor, mitotane, avasimibe, apalutamide, ivosidenib, enzalutamide.
- Strong CYP3A inhibitors: grapefruit juice, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole, troleandomycin, telithromycin, danoprevir, boceprevir, tipranavir, posaconazole, mibefradil, conivaptan, regorafenib, cobicistat, elvitegravir, mifepristone, ceritinib, ribociclib, idelalisib, LCL161, VIEKIRA PAK
- Strong UGT1A inhibitors: atazanavir, gemfibrozil, ketoconazole, indinavir, regorafenib.
- Strong CYP2C8 inhibitors: ketoconazole and other imidazole antifungals, fluoxetine, gemfibrozil, ritonavir, saquinavir, indinavir, nelfinavir, clopidogrel
- Strong CYP2C8 inducers: rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine

Moderate inhibitor and mild inducer

- Moderate CYP3A inhibitor and mild inducer of CYP3A4: aprepitant, fosaprepitant
- Moderate CYP3A inhibitor: netupitant

See for further examples e.g. http://medicine.iupui.edu/CLINPHARM/ddis/clinical-table or https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Arm 1: irinotecan liposomal injection+oxaliplatin+5-FU/LV

Following administration of non-liposomal irinotecan exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in subjects concomitantly receiving the CYP3A enzyme-inducing anticonvulsants phenytoin and strong CYP3A inducers. CYP3A inducers may impact irinotecan liposome injection similarly. Avoid the use of strong CYP3A inducers if possible. Substitute for non-enzyme inducing therapies at least 2 weeks prior to initiation of liposomal irinotecan therapy.

Following administration of non-liposomal irinotecan, subjects receiving concomitant ketoconazole, a CYP3A and UGT1A inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Concomitant administration of aprepitant and fosaprepitant (moderate inhibitors of CYP3A4) with irinotecan should be approached with caution as the combination might result in increased toxicity (neutropenia and diarrhoea). Where anti-emetic options are limited to aprepitant and fosaprepitant, these should only be used based on investigator judgement considering the risk/benefit to the subject. Co-administration of irinotecan liposome injection with CYP3A or UGT1A inhibitors may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A or UGT1A inhibitors if possible. Discontinue strong CYP3A inhibitors at least 1 week prior to starting irinotecan liposome injection therapy. (Data source: irinotecan liposome injection USPI).

Arm 2: nab-paclitaxel+gemcitabine

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A. In the absence of formal clinical drug interaction studies, caution should be exercised when administering nab-paclitaxel concomitantly with CYP2C8 or CYP3A inhibitors or inducers. (Data source: nab-paclitaxel USPI).

Appendix 2 Arm 1 (Irinotecan liposome injection+oxaliplatin+5-FU/LV) Dose Modifications

Prior to each dosing subjects must have:

- ANC ≥2000/mm^3
- Platelet count ≥100,000/mm^3
- Diarrhoea ≤ Grade 1.

Table 9 summarises dose modifications for Arm 1 haematological toxicities, Table 10 summarises dose modifications for Arm 1 diarrhoea, and Table 11 summarises dose modifications for non-haematological toxicities other than diarrhoea, asthenia and Grade 3 anorexia.

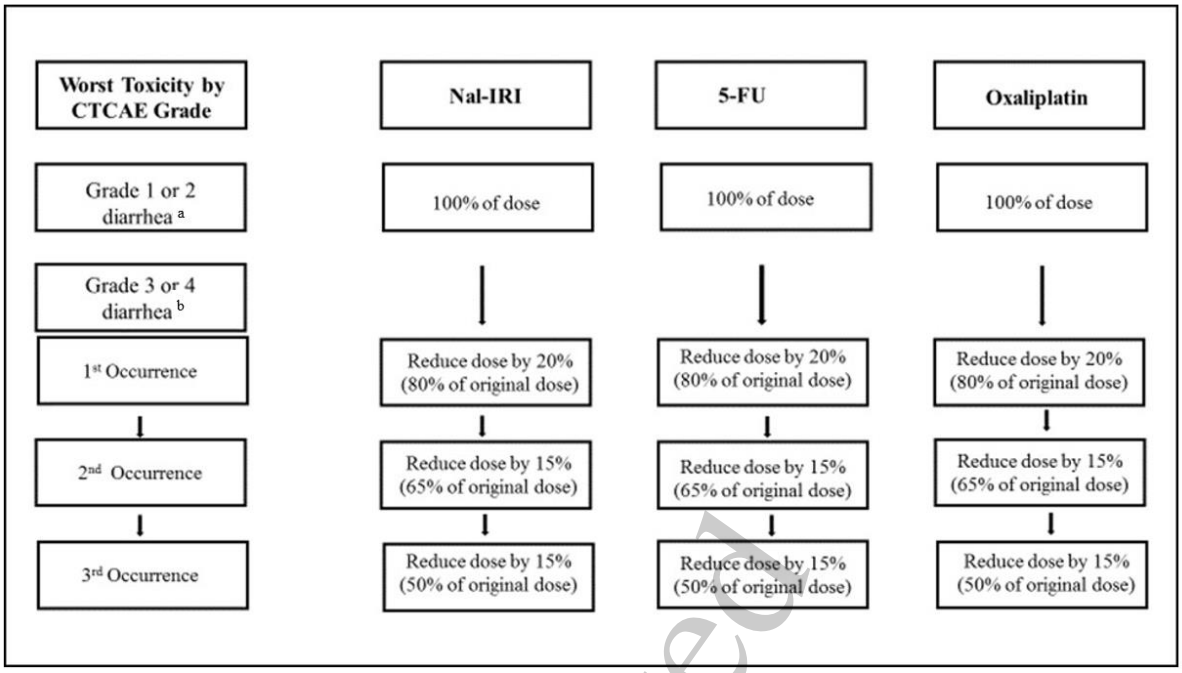
Table 9 Arm 1 (Irinotecan liposome injection+oxaliplatin+5-FU/LV) Dose Modifications for Haematological Toxicities

Worst Toxicity by CTCAE Grade	Irinotecan liposome injection	5-FU	Oxaliplatin	LV
Grade 2 haematotoxicity	100% of previous dose			should remain at the same dose level throughout the study
Grade 3- 4 neutropenia (ANC <1000/mm^3) or febrile neutropenia and/or thrombocytopenia	1st occurrence: Reduce original dose by 20% (80% of original dose) 2nd occurrence: Reduce original dose by another 15% (65% of original dose) 3rd occurrence: Reduce original dose by another 15% (50% of original dose)			
Other Grade 3 or 4 haematologic toxicities not specifically listed above	1st occurrence: Reduce original dose by 20% (80% of original dose) 2nd occurrence: Reduce original dose by another 15% (65% of original dose) 3rd occurrence: Reduce original dose by another 15% (50% of original dose)			

5-FU=5-fluorouracil, ANC=absolute neutrophil count, CTCAE=Common Terminology Criteria for Adverse Events, G-CSF=Granulocyte-colony stimulating factor, LV=leucovorin

Note: Any toxicity ≥ Grade 2 can justify a dose reduction if medically indicated following above guidance. At the discretion of investigator, study discontinuation can occur prior to 3 dose reductions if risk of potential recurrence of febrile neutropenia/neutropenia is considered too high. Subjects who require more than 3 dose reductions must discontinue study treatment. Primary prophylactic use of G-CSF should be considered if subjects are considered high risk in the opinion of the investigator. Secondary prophylactic use of G-CSF after one episode of febrile neutropenia, infection associated with neutropenia and neutropenic sepsis should be considered.

Table 10 Arm 1 (Irinotecan liposome injection+oxaliplatin+5-FU/LV) Dose Modifications for Diarrhoea



5-FU=5-fluorouracil, LV=leucovorin, Nal-IRI=irinotecan liposome injection,

Note: Any toxicity ≥ Grade 2 can justify a dose reduction if medically indicated following above guidance. Subjects who require more than 3 dose reductions must discontinue study treatment. Prophylactic or therapeutic administration of atropine should be considered in subjects experiencing cholinergic symptoms (acute diarrhoea and abdominal cramps during or within 24 hours after nal-IRI administration).

LV should remain at the same dose level throughout the study.

a Grade 1 diarrhoea: <4 stools/day > pretreatment; Grade 2 diarrhoea: 4-6 stools/day > pretreatment.

b Grade 3 diarrhoea: ≥7 stools/day > pretreatment; Grade 4 diarrhoea: life threatening consequences.

Table 11 Dose Modifications for Non-Haematological Toxicities Other than Diarrhoea, Asthenia and Grade 3 Anorexia

<table>
<tr><th>Worst Toxicity by CTCAE Grade</th><th>Irinotecan liposome injection</th><th>5-FU</th><th>Oxaliplatin</th><th>LV</th></tr>
<tr><td>Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy[a]</td><td colspan="3">Optimise anti-emetic therapy AND
1st occurrence: Reduce original dose by 20%
(80% of original dose)
2nd occurrence: Reduce original dose by another 15%
(65% of original dose)
3rd occurrence: Reduce original dose by another 15%
(50% of original dose)</td><td rowspan="8">should remain at the same dose level throughout the study</td></tr>
<tr><td>Grade 2 hand foot syndrome</td><td>100% of previous dose[b]</td><td>1st occurrence:
Reduce original dose by 20%
(80% of original dose)
2nd occurrence: Reduce original dose by another 15%
(65% of original dose)
3rd occurrence: Reduce original dose by another 15%
(50% of original dose)</td><td>100% of previous dose[b]</td></tr>
<tr><td>Grade 3 or 4 hand foot syndrome</td><td colspan="3">Discontinue study therapy</td></tr>
<tr><td>Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity</td><td colspan="3">Discontinue study therapy</td></tr>
<tr><td>Sensory neuropathy</td><td>100% of previous dose[b]</td><td>100% of previous dose[b]</td><td><u>Grade 2, persistent:</u>
Reduce original dose by 20%
(80% of original dose)
<u>Grade 3, recovers prior to next cycle:</u>
Reduce original dose by 35%
(65% of original dose)
<u>Grade 3, recurrent</u>:
Reduce original dose by another 15%[c]
(50% of original dose)
<u>Grade 3 persistent or Grade 4:</u>
Discontinue therapy[d]</td></tr>
<tr><td>Grade 3 or 4 hepatic, renal, respiratory or other toxicities</td><td colspan="3">1st occurrence: Reduce original dose by 20%
(80% of original dose)
2nd occurrence: Reduce original dose by another 15%
(65% of original dose)
3rd occurrence: Reduce original dose by another 15%
(50% of original dose)</td></tr>
</table>

5-FU=5-fluorouracil, LV=leucovorin
Note: Asthenia and Grade 3 Anorexia do not require dose modification. Subjects who require more than three dose reductions must discontinue study treatment. Any toxicity ≥ Grade 2, except asthenia and alopecia, can justify a dose reduction if medically indicated.

a Recommend dose reduction if not resolved to Grade 1 or 2 after a maximum of 5 days of i.v. anti-emetic treatment
b Any toxicity ≥ Grade 2, except asthenia and alopecia, can justify a dose reduction if medically indicated
c At the discretion of the investigator, subjects can discontinue oxaliplatin therapy if Grade 3 persistent sensory neuropathy occurs.

d Subjects who discontinue therapy due to oxaliplatin-related neuropathy may remain on study and continue to receive irinotecan liposome injection+5-FU/LV

Appendix 3 Arm 2 (Nab-paclitaxel+Gemcitabine) Dose Modifications

Prior to each cycle, subjects must have:

- ANC ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Diarrhoea ≤ Grade 1.

Two levels of dose modifications are permitted according to the criteria described below. If a toxicity requiring dose modification occurs following the second dose reduction of either study medication, further treatment should be discontinued. Any further dose modification requires prior sponsor approval. Subjects experiencing study medication-related toxicities that require a delay in scheduled nab-paclitaxel or gemcitabine dosing for more than 21 days will be discontinued from further treatment in this study.

When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment (with the exception that on Day 15, re-escalation with G-CSF support is permitted, after a previous dose reduction on Day 8 of the same cycle).

Dose level reductions required due to toxicity related to nab-paclitaxel and gemcitabine should be made following the guidelines outlined in Table 12.

Table 12 Dose Level Reductions for Nab-paclitaxel and Gemcitabine

Dose Level	Nab-paclitaxel (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction[b]	75	600
If additional dose reductions required	Discontinue study therapy	Discontinue study therapy

a Dose reductions may or may not be concomitant. Please refer to Table 13 and Table 14 for specific recommendations regarding dose modifications within a cycle for hematologic and non-hematologic toxicities, respectively.
b A maximum of 2 dose level reductions are allowed.

Recommended dose modifications for neutropenia and thrombocytopenia are provided in Table 13 and adjustments related to other toxicities are provided in Table 14.

Table 13 Nab-paclitaxel and Gemcitabine Dose Modifications at the Start of Each Cycle or Within a Cycle for Neutropenia and/or Thrombocytopenia

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Nab-paclitaxel/Gemcitabine
Day 1	<1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold therapy [a]
Day 15: IF day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold therapy
Day 15: IF day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold therapy

ANC = absolute neutrophil count
Primary prophylactic use of G-CSF should be considered if subjects are considered high risk in the opinion of the investigator. Secondary prophylactic use of G-CSF after one episode of febrile neutropenia, infection associated with neutropenia and neutropenic sepsis should be considered.
See Section 6.2.5.2 for the maximum interval of delay allowed between doses.
a If Day 8 is delayed, this dose should be omitted and the next dose scheduled for Day15.

Table 14 Nab-paclitaxel and Gemcitabine Dose Modifications for Other Adverse Drug Events

Adverse Drug Reaction	Nab-paclitaxel	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥1500 cells/mm^3; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhoea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

ANC = absolute neutrophil count
Data source: nab-paclitaxel USPI
Primary prophylactic use of G-CSF should be considered if subjects are considered high risk in the opinion of the investigator. Secondary prophylactic use of G-CSF after one episode of febrile neutropenia, infection associated with neutropenia and neutropenic sepsis should be considered.

Peripheral Neuropathy

Nab-paclitaxel treatment should be withheld in subjects who experience ≥Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. Nab-paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤Grade 1. Subjects experiencing peripheral neuropathy that requires a delay in scheduled nab-paclitaxel dosing for ≥21 days will discontinue study treatment. The time to resolution to Grade ≤1 should be the AE duration used for AE reporting.

Cutaneous Toxicity

Subjects who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level for both drugs. If the subject continues to experience these reactions, despite dose reduction, treatment should be discontinued. Subjects who develop Grade 4 cutaneous toxicity should have treatment discontinued.

Gastrointestinal Toxicity

If Grade 3 mucositis or diarrhoea occurs, study medication should be withheld until resolution to ≤Grade 1, then reinstituted at the next lower dose level of both drugs. Subjects who develop Grade 4 mucositis or diarrhoea should have treatment discontinued.

Pulmonary Embolism

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular-weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

Interstitial Pneumonitis

During study participation, subjects should be carefully monitored for signs and symptoms of pneumonitis (i.e. episodes of transient or repeated dyspnoea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasising the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). Study medication administration should be permanently discontinued upon making a diagnosis of interstitial pneumonitis.

Hypersensitivity Reactions

Hypersensitivity reactions are not expected with either nab-paclitaxel or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnoea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema, or

generalised urticaria require immediate discontinuation of study medication administration and aggressive symptomatic therapy.

Subjects who develop a severe hypersensitivity reaction should not be re-challenged.

Appendix 4 Recommended Birth Control Methods for Women of Child Bearing Potential (WOCBP)

Below is a guideline which lists contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, and are considered as highly effective birth control methods, as published by the Clinical Trials Facilitation Group:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[a]
- intrauterine device (IUD)[a]
- intrauterine hormone-releasing system (IUS)[a]
- bilateral tubal occlusion[a]
- vasectomised partner[a,b]
- sexual abstinence[c]

[a] Contraception methods that in the context of this guidance are considered to have low user dependency.

[b] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[c] In the context of this guidance 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

Note: A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation 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 postmenopausal 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.

Appendix 5 Recommendations for Management of Chemotherapy Induced Diarrhoea

Proposed algorithm for the assessment and management of treatment-induced diarrhoea is provided below in Table 15. These guidelines are adapted from those developed by an American Society of Clinical Oncology (ASCO) panel and ESMO Clinical Practice Guidelines for treating chemotherapy-induced diarrhoea [Benson 2004, Utaris 2015, Bossi 2018]. Also Appendix 2, Table 10 for Arm 1 management of dose modifications.

Anti-diarrhoea management should be initiated at the first episode of poorly formed or loose stools or the earliest onset of bowel movements that are more frequent than normal.

Table 15 Recommendations for Management of Chemotherapy Induced Diarrhoea

Dietetic	
Dietetic Measures (applicable for all grades of diarrhoea) Stop all lactose-containing products Drink 8 to 10 large glasses of clear liquids per day Eat frequent small meals Recommend low-fat diet enriched with bananas, rice, apple sauce and toast i.e. BRAT diet	
Fluid Intake Approximately 2L should be maintained Ensure appropriate fluid and electrolyte replacement	
Pharmacological Treatment	
First Line Therapy: loperamide	
Clinical Presentation	**Intervention**
If receiving prophylaxis:	Increase loperamide dose to a maximum of 16 mg/day. Continue until diarrhoea free for 12 hours. If no improvement within 48 hours implement second-line therapy.
If new-onset diarrhoea:	Take loperamide 4 mg with first bout of diarrhoea followed by 2 mg every 4 hours or after every unformed stool (maximum 16 mg/day). Continue until diarrhoea free for 12 hours. If no improvement within 48 hours implement second-line therapy.
With recovery to ≤Grade 1:	Take loperamide 4 mg one dose with each subsequent cycle of irinotecan liposome injection administration.
Second Line Therapy	
Grade 1 If persistent diarrhoea on loperamide:	Add diphenoxylate, hydrochloride plus atropine suffate (Lotomil®) 2.5 mg every 6-8 hours. Monitor for trend in decreasing WBC and/or neutropenia. Recommend G-CSF if decreasing WBC and/or neutropenia to avoid infectious/septic complications. See Section 6.3.3.
Grade 2 If persistent diarrhoea on loperamide:	Add octreotide (short acting) 150 µg subcutaneously tid or after initial dose of short acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg intramuscularly. Monitor for trend in decreasing WBC and/or neutropenia. Recommend G-CSF if decreasing WBC and/or neutropenia to avoid infectious/septic complications. See Section 6.3.3. Consider stool cultures to exclude infectious causes (e.g. Clostridium difficile) prior to prophylactic antibiotics, especially if diarrhoea is persistent beyond 24 hours or if there is a fever or Grade 3 or 4 neutropenia

Grade 3/4 After intensive loperamide therapy:	Titrate loperamide to keep diarrhoea controlled (<4 stools/day). Octreotide (100 to 150 µg subcutaneously bid or 25 to 50 µg/hour intravenously if dehydration is severe, with dose escalation up to 500µg subcutaneously tid). Intravenous fluids as appropriate. Consider prophylactic antibiotics, especially if diarrhoea is persistent beyond 24 hours or if there is a fever or Grade 3 or 4 neutropenia. Stool cultures to exclude infectious causes. Monitor for trend in decreasing WBC and/or neutropenia. Recommend G-CSF if decreasing WBC and/or neutropenia to avoid infectious/septic complications. See Section 6.3.3 Consider stool cultures to exclude infectious causes (e.g. Clostridium difficile) prior to prophylactic antibiotics, especially if diarrhoea is persistent beyond 24 hours or if there is a fever or Grade 3 or 4 neutropenia

Appendix 6 ECOG Performance Status

Grade	ECOG Performance Status[a]
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 self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

[a] Published by Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

Appendix 7 Dihydropyrimidine Dehydrogenase (DPD) Testing Requirements

Requirements for France

The Haute Autorité de Santé (HAS) (French National Authority for Health) and the Institut National du Cancer (INCa) (French National Cancer Institute) recommend testing for DPD deficiency by determination of uracil plasma concentration (uracilemia) where fluoropyrimidine treatment is planned.

This test is recommended in the following conditions:

- pre-analytical conditions: use of blood collection tubes without separator gel and with anticoagulant, maximum delay between sample and centrifugation 1 hour 30 minutes if the sample is stored at ambient temperature, and 4 hours if it is stored at +4°C, centrifugation preferably at +4°C then immediate freezing of the resulting plasma, transport respecting the cold chain,
- assay technique: by high or ultra-high performance liquid chromatography (several possible detection modalities).

Failure to comply with these conditions must lead to a report of non-compliance brought to the attention of the clinician as soon as possible so that a new sample can be sent to the laboratory quickly.

- interpretation and expression of the results:
  - uracilemia ≥150 ng/ml suggests complete DPD deficiency
  - uracilemia ≥16 ng/ml and <150 ng/ml suggests partial DPD deficiency
- interpretation of the results on the basis of these threshold values must take account the fact that uracilemia is a continuous variable and that the risk of severe toxicity increases therefore theoretically as uracilemia increases.

Subjects with low or absent DPD activity (complete deficiency i.e. blood uracil level ≥150 ng/ml and partial deficiency i.e. blood uracil level between ≥16 ng/ml and <150 ng/ml) will not be eligible for inclusion in this study.

Appendix 8 Temporary Measures and Procedures Related to COVID-19 Pandemic

This appendix is intended to provide temporary measures to manage study assessments that cannot be done in compliance with the current protocol version approved at your site, because of the COVID-19 pandemic.

The implementation of the below measures must be in line with applicable country regulation or national temporary COVID-19 measures guidance and must remain temporary until situation resolves, at which point the protocol assessments will return to those specified in the current approved protocol effective at that time. The temporary measures may remain in place for differing periods of time per country/site.

The temporary measures specified in the appendix must be reported as deviation related to COVID-19 and must still be documented and reported to the ECs/IRB and/or Health Authorities, based on the regulatory requirements applicable at your country/site, in addition to any deviation to the current protocol.

Investigators will determine the feasibility of starting or continuing study treatment on a subject-by-subject basis, depending on the ability to conduct safety monitoring and providing subjects an adequate supply of study treatment, in accordance with local requirements.

Specific Guidance for Study Visits and Assessments

Study Schedule

If the COVID-19 pandemic prevents subjects from coming to the site, subjects can have their study visit assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor or delegate before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the subject's general practitioner or specialist physician to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments is provided below.

The IECs/IRBs will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

Screening and Enrolment

Subjects cannot be screened more than once. However, if a subject tests positive for COVID-19 during the screening period, this should be escalated to the sponsor (or delegate), in case an extension of the screening period is required for the subject to recover. In exceptional circumstances, where a subject starts screening procedures, which are then delayed due to COVID-19 (for example testing positive for COVID-19), the subject might continue with the screening assessment once a negative test is confirmed to confirm all eligibility criteria are met prior to randomisation, even if this is outside the normal 28-day screening window, after discussion with the sponsor (or delegate).

Informed Consent (including Re-consent)

As per guidelines issued by the FDA in the US and in line with guidance in other countries, the use of electronic signatures is authorised to obtain the subject's informed consent. The sponsor and IRB need to be notified of the use of electronic informed consent signature and the accepted electronic formats need to be clearly documented. This is not meant to replace the important discussion between the subject, investigator and site staff. Such a discussion must still occur and be part of a screening visit (in-person, by telemedicine, or home health visit). A clearly

documented process on how subjects are contacted virtually to explain the study and close monitoring needs to be in place.

Screening visit and assessments (apart from informed consent as described above) must be performed on site.

Dosing Visits (Arm 1 and Arm 2)

In case of dosing visit delayed due to COVID-19 (temporary closure of the site, subject unable to travel etc).

- Dose delay rules should be followed as per last protocol version approved at your site. In case of dosing visit delays outside of the protocol, these should be discussed between the investigator and the sponsor or delegate

In case of suspected COVID-19 infection

- The administration of study medication may be temporarily discontinued depending on the patient clinical presentation. In some cases, the investigator may request a subject be retested before the administration of study treatment is resumed.
- In all cases, the investigator must ensure that the subject receives appropriate medical follow-up. It will be in the PI's medical judgement to assess the benefit and risks of restarting study treatment. If a subject has temporarily discontinued study treatment, the decision to restart subjects on study treatment will be managed on an individual subject basis in discussion with the sponsor (or delegate) and investigator.

In case of confirmed COVID-19 infection

- Subjects who presents with COVID-19 positive-confirmed infection should be placed on immediate study treatment delay as per institutional guidelines [Curigliano 2020]. In addition, any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection should be considered serious and be immediately reported to the sponsor.
- Since there is lack of data on risk/benefit analysis of the study treatment arms and COVID-19 infection, in the absence of a confirmatory negative COVID-19 PCR test in an asymptomatic subject, it is in the investigator's medical judgement to assess the benefit and risks of restarting study treatment. The management of subjects following this quarantine period and decision to restart subjects on study treatment will be managed on an individual subject basis in discussion with the sponsor (or delegate) and investigator.
- In addition to the above criteria, any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection should be considered serious and be immediately reported to the sponsor. The seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation).

Physical Examinations and ECOG Performance Status

Assessment can be done via telemedicine (as per the rules below) and should be done according to local practice.

Quality of Life Assessments

The subject has access to the ePRO application via their own devices (mobile phone, tablet) via an electronic application. Site staff are to ensure this has been set up for a subject and provide training where required. If the subject is unable to use the application on their own then the information can be collected via a telephone call; the site staff will call the subject, ask the questions as per the assessment in exactly the same order and wording (paraphrasing is not allowed) and directly enter the data into the eCRF on behalf of the subject. Answers to questions must not be noted down first and then entered into the eCRF as this could impact validation of

the ePRO tool. Details of the verification of the patient and the site personnel conducting the assessment should be documented.

Disease Evaluation: CT/MRI Scans

This study assessment does not always coincide with a dosing day, though it might coincide if the subject has had no dosing delays (e.g. due to toxicity). In the case where the assessment does not coincide with a dosing visit, to reduce the risk associated with travelling to a study site, imaging may be performed at a local imaging facility. The modality to be used for the imaging is to be documented and shared with the local imaging facility. The same imaging modality must be used to ensure consistency and secure central reading. Also, central reading requires that consistent slide thickness (deemed acceptable <5mm) and same methodology (with vs without contrast agent) across acquisitions timepoints is met. Please secure scan modality slide thickness and methodology used from baseline are shared with local imaging facility.

Documentation of the imaging facility is to be collected by the site and retained. Scanned images are to be shared with the site. The site is responsible for submitting scans for Medpace Imaging Central Laboratory. The RECIST reading is to be done by the investigator for treatment choices. The local facility must be informed about potential queries that may be sent from the central reader after image upload by the main site. These queries may need to be addressed by the local imaging facility. A clear process should be documented in writing to explain how the queries issued from central image QC will be managed between the local facility and the site.

Sample Collection

Haematology and Biochemistry: To reduce the risk associated with travel to the site if the patient comes in the day prior to dosing for haematology sampling, or to reduce the risk associated with time the subject spends at the study site, a local laboratory may be used to obtain and analyse the haematology samples. Results of haematology samples taken need to be shared with the investigational site and assessed prior to dosing as per protocol requirements. Documentation of the local laboratory (accreditation and reference ranges) are required to be collected and shared with the sponsor. As the subject attends the site for dosing, effort should be made to collect biochemistry samples for central laboratory assessment, as well as all other central laboratory samples. If this is not possible, local biochemistry samples are to be collected as described above.

Pregnancy Test: Pregnancy testing is required on Day 1 of each cycle. To reduce the risk associated with travel to the site, if the subject comes in the day prior to dosing for pregnancy testing, or to reduce the risk associated with time the subject spends at the study site, a local laboratory, hospital or general medical practice may be used to obtain the pregnancy test. Results of the pregnancy test need to be shared with the investigational site and assessed prior to dosing as per protocol requirements.

Arm 1: 5-FU Pump Removal

To reduce the risk associated with travel to site, pump removal can be performed at home, a local hospital or at a general medical practice. In case of a home visit, the patient must agree that someone will visit them at home for this pump removal. Agreement between the study site and the responsible personnel removing the pump needs to be in place, including documentation of how information will be shared, and must be in line with local regulations with regards to privacy and confidentiality. Details of the time of pump removal must be shared by the responsible personnel with the site. The site staff should call the subject on the day of the pump removal to discuss the medications the subject may be taking as well as any AE updates since the previous visit. Details of the verification of the identity of the subject and the site personnel conducting the assessments (both the pump removal as well as the phone call) must be

documented. In case of home removal of the 5-FU pump, PK samples that will not be collected will have to be reported as deviation.

Concomitant Medications and Procedures

Details can be collected by site staff via telephone call as per the rules relating to use of telemedicine below.

COVID-19 vaccines and or medication shall be reported as concomitant medication.

AE Reporting

Of note, as per protocol Section 8.1.5, all COVID-19 cases (suspected or confirmed) should be considered as Serious Adverse Events.

"Other Medically significant" should be selected as seriousness criterium if no other seriousness criteria are present (e.g. hospitalisation).

Details can be collected by site staff via telephone call as per the rules relating to use of telemedicine below.

Note that further information about measures adopted for the COVID-19 situation to cover SAE reporting and temporary discontinuations are found in Sections 8.1.5 and 8.1.8, respectively.

Specific Rules Relating to use of Telemedicine

The form of telemedicine used (phone call or use of a platform), the legal and privacy protection of the subjects as well as details of the verification of the identity of the subject and site personnel conducting the assessment should be documented at site level and should be available for review by the monitor.

Source Data Verification

When remote data monitoring is allowed per local regulations/national guidance and possible at site, PI or delegate must:

- document in the source documents verbal consent from their subject for remote monitoring of their data by the sponsor during the pandemic

  or

- obtain written consent from their subject for remote monitoring of their data if required by local regulations and/or "on site" monitoring of subject data is specified in the local ICF.

Guidance on COVID-19 Vaccine and/or Medication

Currently available COVID-19 vaccines do not contain live virus; therefore, they are permitted during the study period.

Future approved COVID-19 vaccines and or medication will be assessed by the Sponsor.

Subjects may receive COVID-19 vaccination if they have no contraindications to any component of the specific vaccine. However, they should be counselled by the investigator about benefit/risk of getting the vaccination based on their individual health conditions as well as with the healthcare physician administrating the vaccination, about the unknown vaccine safety profile and effectiveness in immunocompromised populations, as well as the potential for insufficient immune responses, and the need to continue to follow all current guidance to protect themselves against COVID-19.

The co-administration of the COVID-19 vaccines with study treatment has not been studied. Based on the lack of evidence following is recommended [Desai 2021]:

- Avoiding administration of study treatment within 48 to 72 hours of vaccination to minimize confusion and/or inaccurate attribution of adverse event causation.

- On study treatment: patients can be vaccinated between cycles of intermittent cytotoxic chemotherapy 1 to 2 weeks before or 1 to 2 weeks after drug dose, when possible, to increase the potential for the immune system to mount a response.

Investigator discretion is necessary to ascertain benefit/risk taking into consideration subject's clinical condition. COVID-19 vaccines and or medication shall be reported as concomitant medication.