MM-398-07-02-03: A Randomized, Open-label Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI)-containing Regimens *versus* nab-paclitaxel plus Gemcitabine in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma

IPSEN BIOSCIENCE, Inc.

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Sponsor:
IPSEN BIOSCIENCE, Inc.
650 East Kendall Street,
Cambridge MA 02142
USA

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SUMMARY OF CHANGES

The current version of the protocol (Version 7.0) was released on 27 September 2019. This protocol version includes all amendments, with summaries of changes from Version 3.1 included in the following appendices. The main purpose of this amendment is to amend details of the extension part of the study (see Appendix 8).

- Appendix 5: Summary of Changes 28 December 2016 (Version 3.1) to 29 September 2017 (Version 5.0)
- Appendix 6: Summary of Changes: 03 April 2017 (Version 4.0) to 29 September 2017 (Version 5.0).
- Appendix 7: Summary of Changes 29 September 2017 (Version 5.0) to 11 April 2018 (Version 6.0)
- Appendix 8: Summary of Changes 11 April 2018 (Version 6.0) to 27 September 2019 (Version 7.0)

The changes for all these amendments were substantial.

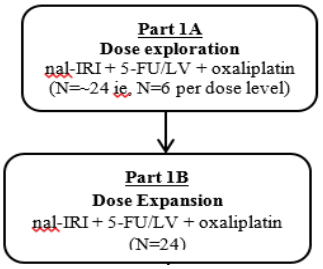
LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	5-Fluorouracil
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
ASCO	American Society of Clinical Oncology
BOR	Best overall response
BUN	Blood urea nitrogen
CA19-9	Carbohydrate antigen 19-9
CBC	Complete blood count
C_{max}	Maximum concentration
CR	Complete response
CRF	Case report forms
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCR	Disease control rate
DLT	Dose limiting toxicity
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EPR	Enhanced permeability and retention
EU	European Union
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factors
HIV	Human immunodeficiency virus
ICH	International Conference on harmonization
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
Kg	Kilogram
KPS	Karnofsky Performance Status
L	Liter
LDH	Lactate dehydrogenase
LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose

Abbreviation	Definition
MUGA	Multiple gated acquisition scan
nal-IRI	Nanoliposomal irinotecan; MM-398
NCI	National Cancer Institute
ng	Nanogram
nm	Nanometer
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetic
PFS	Progression free survival
PR	Partial response
PS	Performance Status
QTcF	QT interval, Fridericia correction
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
$t_{1/2}$	Half-life
TOP-1	Topoisomerase-1
TAM	Tumor associated macrophages
UDP	Uridine diphosphate
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
Vss	Volume at steady state
WBC	White blood count

STUDY SYNOPSIS

Sponsor	Ipsen Bioscience, Inc
Protocol Title	A randomized, open-label, Phase 2 study of nanoliposomal irinotecan (nal-IRI)-containing regimens versus nab-paclitaxel plus gemcitabine in patients with previously untreated, metastatic pancreatic adenocarcinoma
Protocol Number	MM-398-07-02-03
Phase of Development	Phase 2
Trial Location:	International; multiple sites
Rationale	Nal-IRI (also known as MM-398) is a nanoliposomal formulation designed to deliver irinotecan to the tumor microenvironment for local drug activation. In a randomized phase 3 study, patients with metastatic pancreatic cancer who had progressed following gemcitabine-based therapy (the NAPOLI-1 study), nal-IRI in combination with 5-FU/LV demonstrated significant clinical activity, increasing OS and progression free survival (PFS) relative to 5-FU/LV. The goal of this current study is to assess the safety, tolerability and preliminary efficacy of nal-IRI in combination with 5-FU/LV and oxaliplatin in patients not previously treated for metastatic pancreatic adenocarcinoma to select a regimen for further development.
Primary Objective	The study primary objectives are: • To evaluate the safety and tolerability of nal-IRI + 5-FU/LV + oxaliplatin • To characterize dose-limiting toxicities (DLTs) associated with nal-IRI + 5-FU/LV + oxaliplatin and determine the recommended dose of the triplet combination for future development
Secondary Objectives	• To characterize the pharmacokinetics (PK) of nal-IRI in combination with 5-FU + oxaliplatin • To evaluate efficacy signals with nal-IRI in combination with 5-FU/LV + oxaliplatin using overall response rate (ORR) [CR + PR, per RECIST v1.1], disease control rate (DCR) [CR + PR + SD, per RECIST v1.1], duration of response, PFS, and OS
Exploratory Objectives	• To evaluate the relationship between plasma PK of nal-IRI (total irinotecan, SN-38) in combination with 5-FU and oxaliplatin, and safety and efficacy endpoints in first-line metastatic pancreatic cancer • To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI in combination with 5-FU/LV and oxaliplatin, PK, toxicity, and/or response
Study Design	This is an open-label, Phase 2 study to assess the safety, tolerability, and preliminary efficacy of nal-IRI in combination with 5- FU/LV and oxaliplatin in patients not previously treated for metastatic pancreatic adenocarcinoma. The study will be conducted, as illustrated in the schematic below, with an initial dose exploration (Part 1A) followed by dose expansion (Part 1B) of the nal-IRI + 5-FU/LV + oxaliplatin regimen.



In Part 1A, safety and tolerability will be evaluated across a range of oxaliplatin and nal-IRI dose permutations, as summarized in the table below. Oxaliplatin will be administered at intended dose levels of 60 mg/m^2 - 85 mg/m^2 IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. Nal-IRI will be administered at a dose range of 60 mg/m^2 – 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each cycle. 5-FU and leucovorin will be administered at fixed dose levels (2400 and 400 mg/m^2 respectively) for all dose level cohorts.

Dose Level*	Dose Day	Oxaliplatin (mg/m^2)	5-FU/LV (mg/m^2)	Nal-IRI (mg/m^2)[a]
1	1, 15	60	2400/400	80
-1	1, 15	60	2400/400	60
2	CCI			
-2A				
-2B	1, 15	85	2400/400	60
-3	1, 15	70	2400/400	65

[a] Nal-IRI the dose is calculated in salt base.
Note: Dose level specifics and dose de-escalation plans are presented in protocol Section 4.1.

The original plan in the study was to evaluate dose levels as described in the table above. Dose level cohorts 1, -1 and -2B have been evaluated. Dose levels 1 and -2B were considered to be not tolerable. Dose level -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable. Following the completion of the three predefined dose level cohorts, a new dose level -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) was introduced following a protocol amendment (protocol Version 5.0) to evaluate its safety and tolerability. Dose levels 2 and -2A were considered not to be evaluated in the study. Prior to this Version 5.0, the enrollment of dose level cohorts 1, -1 and -2B had been completed.

Patients will be enrolled in cohorts following a 3 + 3 dose escalation design in Part 1A, in order to select the dose level of the combination of oxaliplatin and nal-IRI to be used in Part 1B (dose expansion). Dose limiting toxicities (DLTs) will be assessed during the safety evaluation period (i.e. 28 days in Cycle 1; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to Section 6.5).

Safety evaluations are to be conducted regularly by the DLT committee to review all SAEs, AEs and DLTs for each patient to determine the safety and tolerability in each Cohort. The DLT Committee is comprised of the Investigators, the Medical Monitor, and the Sponsor.

	In the absence of DLT, a minimum of 3 patients will be treated within each dose level cohort for a minimum of one cycle of therapy. Additional patients will be recruited into a cohort according to the DLT provisions outlined below, or if non-DLT toxicity is identified as requiring further evaluation by the DLT Committee. In each dose level cohort, if there are no DLTs within the safety evaluation period, then additional dose level cohorts will be initiated following agreement by the DLT Committee. If one DLT occurs within the first 3 patients in a given dose level cohort, then the cohort will be expanded to a minimum of 6 patients. If 2 or more patients have DLTs within a given dose level cohort, that cohort will be considered to have not met the safety and tolerability criteria of the combination, and the cohort will stop. As DLT within any cohort is potentially determined by a complex interaction between the respective dose levels of oxaliplatin and nal-IRI, the sequence of cohorts examined (dose levels -1 to -3) contains both dose escalation and dose de-escalation strategies for each individual drug, in order to control the total combined dose level within any given cohort. This means that for each individual drug, the dose level may decrease, increase or remain the same between successive cohorts. At the completion of the safety evaluation period (as defined in Section 3.2.2) for the last patient enrolled for dose level cohorts -1 to -3 (Part 1A) detailed in Table 5, all available data (DLT, SAE, and grade 3-4 adverse events, any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data) are reviewed by the DLT Committee. A dose level will be selected for expansion (Part 1B as described below). The expansion cohort is intended to enroll 24 additional patients (total of 30 patients for the selected dose level) to obtain additional safety and efficacy data. • If the dose level cohort -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) is considered to meet the safety and tolerability criteria, this dose will be selected for expansion. • If the dose level cohort -3 is not considered to meet the defined safety and tolerability criteria, the dose level cohort -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) will be selected for expansion. No DLT assessment will be conducted for the expansion cohort. Final determination of an appropriate combination regimen for potential future development will be made after all patients in the Part 1A (dose escalation) and Part 1B (expansion cohort) have completed two scheduled assessments (approximately 16 weeks of therapy; unless withdrawn at an earlier time point due to disease progression or drug-related toxicity) and will take into account all available data from the expansion cohort and also all available updated data for patients still receiving ongoing therapy in the other dose level cohorts. Data will include DLT, SAE, and grade 3-4 adverse events along with any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data. **Dose Limiting Toxicity** The following adverse events will be considered as DLTs if they occur during the safety evaluation period and are deemed related to the study treatment regimen: • Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal therapy (withholding study drug and

	administering concomitant medication, e.g. G-CSF administration for neutropenia) • Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection • Any study regimen related adverse event that leads to a delay of the next scheduled study treatment dose for more than 14 days • Any grade 4 non-hematologic toxicity with the specific exclusion of: o Fatigue/asthenia < 2 weeks in duration o Increases in alkaline phosphatase levels o Nausea and vomiting ≤ 3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen) o Diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen) Any adverse event that is related to disease progression will not be considered a DLT. To be DLT evaluable, a patient should have received both doses of study medication at Cycle 1. A delay of up to 14 additional days (a total of 28 days) is permitted between the scheduled Day 1 and Day 15 administrations due to non-DLT drug related toxicity. For Part 1A (dose level cohorts -1 to -3), any patient requiring a dose delay of >14 days during the safety evaluation period due to non-drug related reasons will be replaced for DLT evaluation purposes. Any patient not receiving both doses of study drug during the safety evaluation period, for reasons other than dose limiting toxicity, will be replaced for DLT evaluation purposes. For Part 1B (the expansion period) patients withdrawing from treatment with study medication will not be replaced. All patients will continue to be monitored for safety beyond Cycle 1, in order to determine if multiple cycles of treatment are tolerable. If a patient within a given cohort experiences a DLT in Part 1A, they may continue in the study at a lower dose level of oxaliplatin and/or nal-IRI, (as determined by the DLT Committee, in accordance with Section 6.5) upon resolution of the relevant toxicity. Other patients in the same cohort who do not experience a DLT will continue with unmodified dose levels of oxaliplatin and/or irinotecan (unless a dose modification is judged to be necessary by the DLT Committee on safety grounds). In Part 1A and Part 1B, patients within any given cohort will remain on the dose levels of oxaliplatin and nal-IRI they were originally allocated to. Dose escalation within a cohort will not be permitted, although dose modifications for toxicity will occur in accordance with Section 6.5. **Translational Research** Translational research components will include collection of blood samples and archived tumor (during screening, if available) to look for potential biomarkers. Analyses may include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), or enzyme levels (e.g. MMP9).

Number of Patients	Approximately 54 patients will be enrolled in the study.
Inclusion Criteria	Inclusion Criteria: To be eligible for inclusion into the study patients must meet the following inclusion criteria: a) Histologically or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to Screening b) At least one tumor lesion measurable by CT or MRI scan (according to RECIST v1.1 criteria) c) ECOG performance status of 0 or 1 at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening. Two observers will be required to assess ECOG. If different, the lowest assessment will be used for the eligibility evaluation at each assessment (criterion applicable only for Part 1A) d) Adequate biological parameters as evidenced by all of the following blood counts: • Absolute neutrophil count (ANC) > 1,500 cells/µl without the use of hematopoietic growth factors within last 7 days prior to Screening • Platelet count > 100,000 cells/µl • Hemoglobin > 9 g/dL; transfusion is allowed, provided interval is ≥ 7 days prior to Screening e) Adequate hepatic function as evidenced by: • Serum total bilirubin ≤ ULN (biliary drainage is allowed for biliary obstruction), and • AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present) f) Adequate renal function as evidenced by serum creatinine ≤ 1.5 x ULN, and calculated clearance ≥60 mL/min/1.73 m^2 for patients with serum creatinine levels above or below the institutional normal value. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); for patients with body mass index (BMI) >30 kg/m^2, lean body weight should be used instead g) ECG without any clinically significant findings (e.g. QTc ≤450 ms for males and ≤470 ms for females and no known arrhythmias) h) Recovered from the effects of any prior surgery or radiotherapy i) ≥ 18 years of age j) Inclusion criteria removed (protocol Version 5.0) k) Able to understand and provide an informed consent l) Patient has a Karnofsky performance status (KPS) ≥ 70 at Screening, and within 72 hours prior to date of first dose if first dose occurs more than 72 hours after screening. Two observers will be required to assess KPS. If discrepant, the one with the lowest assessment will be considered true (criterion applicable only for Part 1B, added in protocol Version 6.0)
Exclusion Criteria	Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria: a) Prior treatment of pancreatic cancer in the metastatic setting (or locally advanced setting) with surgery, radiotherapy, chemotherapy or investigational therapy (Note: palliative radiotherapy is permitted; placement of biliary stent is allowed) b) 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 c) Uncontrolled CNS metastases (Note: Patients who require steroids should be on a stable or decreasing dose to be eligible) d) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, diarrhea > grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction e) History of any second malignancy in the last 3 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years. f) Known hypersensitivity to any of the components of nal-IRI, other liposomal products, or any components of 5-FU, leucovorin or oxaliplatin g) Exclusion Criteria removed (protocol Version 6.0) h) Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including: • Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion • NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure • Known historical or active infection with HIV, hepatitis B, or hepatitis C i) 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, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome j) Use of strong CYP3A4 inhibitors or inducers, or strong UGT1A1 inhibitors (patients are ineligible if unable to discontinue the use of strong CYP3A4 or UGT1A1 inhibitors at least 1 week or strong CYP3A4 inducers at least 2 weeks prior to receiving first dose of irinotecan liposome injection), or presence of any other contraindications for irinotecan[1] k) Presence of any contraindications for nal-IRI, 5-FU, leucovorin, or oxaliplatin. l) Exclusion Criteria removed (protocol Version 6.0) m) Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results n) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy within 7 days prior to the first dose based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 6 months following the last dose of study drug[2]. o) Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma p) Documented serum albumin <3 g/dL at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening (both labs at screening and prior to first dose may be confirmed locally) q) Patients 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 r) Previous treatment with irinotecan-based, nab-paclitaxel-based or gemcitabine-based resulting in disease progression (added in protocol Version 6.0)

	[1] See Section 6.8 for examples of strong CYP3A4 or UGT1A1 inhibitors or CYP3A4 inducers. [2] For a description of highly effective contraceptive measures, please see Appendix 1.
Length of Study	All patients in the study will be treated until disease progression, unacceptable drug related toxicity, or physician or patient's choice. A follow up clinic visit is required approximately 30 days after last dose of study treatment to complete the final safety assessments. Subsequently, patients will be followed for survival once every 2 months via telephone, email, or clinic visit until death, lost to follow-up, withdrawal of consent, or study closure, whichever occurs first. Following fulfilment of analysis requirements for the primary and/or secondary endpoints, the sponsor may elect to transition patients that are still receiving treatment or are being followed for OS to an extension phase of the study.
Investigational Product:	Nal-IRI (irinotecan liposome injection; also known as MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. It will be supplied in sterile, single-use vials containing 10 mL of nal-IRI at a concentration of 5 mg/mL. Nal-IRI must be stored refrigerated at 2 to 8°C, with protection from light.
Additional Anti-cancer Therapies:	Patients will be treated with one or more of the following approved therapies: • 5-FU/LV • oxaliplatin Please reference the respective package inserts for additional information.
Dosing Regimen:	The regimen below will be tested in 28-day cycles, unless cycle duration is modified by toxicity in accordance with Section 6.5.3. **nal-IRI + 5-FU/LV + oxaliplatin** • Oxaliplatin will be administered at dose levels as indicated in Table 5 (60 mg/m^2 - 85 mg/m^2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. • Nal-IRI will be administered over a dose range 60 mg/m^2 – 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. • 5-FU will be administered 2400 mg/m^2 IV over 46-hours (±60 minutes), on Days 1 and 15 of each 28-day cycle with leucovorin (l + d racemic form) 400 mg/m^2, IV over 30 minutes (±5 minutes), on Days 1 and 15 of each 28-day cycle. If oxaliplatin is not well tolerated, oxaliplatin may be discontinued and patients may continue to receive nal-IRI + 5-FU/LV at the discretion of the Investigator. Toxicity requiring discontinuation of nal-IRI will result in discontinuation from all study treatments.

Criteria for Evaluation:	**Safety evaluation:** Assessments for safety will include all treated patients and will be based on adverse events, laboratory data, and study treatment related dose-limiting toxicities. **Pharmacokinetic evaluation:** Plasma samples will be analyzed for the concentration of nal-IRI (irinotecan) and its metabolite (SN-38) in order to derive PK parameters of nal-IRI when given in combination with other anticancer therapies. PK parameters of the combination therapies (5-FU and oxaliplatin) will also be determined, where warranted by the data, to evaluate any drug interactions with nal-IRI. **Efficacy evaluation:** Preliminary efficacy will be analyzed descriptively. Efficacy parameters summarized will include DCR at 16 weeks, duration of response, ORR, PFS and OS. **Translational / Exploratory** Archived tumor tissue (if available) and blood samples will be collected and analyzed for biomarkers. Samples will be used to explore potential markers of sensitivity and resistance to irinotecan, which may include, but are not limited to, the following: Topoisomerase-1, growth factor pathways (IGF1 and EGFR family receptors and ligands), and factors involved in CPT-11 conversion to SN-38.
Statistical Analyses:	The safety population will include all patients receiving at least one dose of any study drug. Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum). Tumor evaluation will be measured according to RECIST v1.1. For each patient, PFS time will be determined as the time from the first study drug to the first documented radiographical progression of disease (PD), per investigator using RECIST v1.1, or death from any cause, whichever comes first. If the progression or death occurs at a time point that is greater than 16 weeks after the non-PD last tumor assessment, then progression-free survival time will be censored at the time of the last non-PD tumor assessment. **Efficacy Analysis** PFS will be analyzed using Kaplan-Meier method and descriptively summarized at 3 months interval for each dose level cohort. Median PFS time and corresponding 95% confidence limits will be presented. Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from the first dose of study drug. Overall Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of overall response. The estimates of overall response rate and its corresponding 95% CI will be calculated for each dose level cohort.

	A patient will be classified as having achieved disease control at 16 weeks if the patient has not progressed at the Week 16 assessment, i.e. has no PD up to and including the Week 16 assessment with documented non-PD (SD, PR, or CR) assessment. Patients who die, discontinue tumor assessments, or start new anti-cancer treatment prior to Week 16 will be considered as not having achieved DCR at Week 16. The disease control rate at 16 weeks (DCR_{16}) for a treatment group/cohort will be estimated by the number of patients who achieve disease control at 16 weeks divided by the number of patients treated. Overall Survival (OS) is the time from the date of first study drug to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. Similar to PFS, OS will be analyzed using Kaplan-Meier method and descriptively summarized for each dose level cohort. **Safety Analyses** Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported by the MedDRA Version 17.1 or higher. Toxicity will be graded according to the NCI CTCAE Version 4.03. Safety analysis of patients will include a summary of dose-limiting toxicity events. The period for treatment-emergent adverse events and safety findings will be from the time of first study drug administration to 30 days after the date of last study drug administration. If an adverse event begins on the date of first study drug administration with no time recorded, the event will be considered as treatment-emergent. Tabular summaries will be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study drug discontinuation, TEAE-related to study drug and TEAE Grade 3/4. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient. Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so. Laboratory, vital signs, and ECG data will be summarized according to parameter type. **Pharmacokinetic Analyses** Plasma concentrations of total irinotecan, SN-38, oxaliplatin and 5-FU in the combination therapies will be used to characterize corresponding PK parameters using a nonlinear mixed effects approach. Individual PK parameters will be estimated if warranted by the data. Graphical exploration will be performed to investigate any relationship between PK and pharmacodynamic endpoints. If a trend is shown, PK/PD modelling will be performed and reported separately.

Sample Size Justification:

The total number of patients enrolled in the study will depend on the number of patients examined within each dose level cohort, as determined by the DLT Committee. Progression to the next dose level cohort will depend on the background toxicity rate (i.e., probability of DLT at a given dose level). When 1 of 3 patients develops a DLT and the cohort is expanded to a minimum of 6 patients, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of <10%. The table below shows the probability of escalation from cohort to cohort with various toxicity rates.

Background Toxicity Rate	**1%**	**5%**	**10%**	**20%**	**30%**	**40%**	**50%**
Probability of Dose Escalation	0.999	0.973	0.906	0.709	0.494	0.309	0.172

A selected dose level cohort will be expanded to include 30 patients in total. An estimate of the DCR at Week 16 will be tabulated and summarized. The following table displays the probabilities of outcomes for DCR_{16} with n=30 as a function of the true DCR_{16}:

True DCR_{16}	**Probability observed DCR_{16} ≥ 50%**	**Probability observed DCR_{16} ≥ 55%**	**Probability observed DCR_{16} ≥ 60%**
45%	0.36	0.14	0.07
50%	0.57	0.29	0.18
55%	0.77	0.50	0.36
60%	0.90	0.71	0.58
65%	0.97	0.87	0.78
70%	0.99	0.96	0.92

1 INTRODUCTION

1.1 Pancreatic Cancer

Pancreatic cancer is chemotherapy-resistant, with an extremely poor prognosis. It is the fourth leading cause of cancer death in the United States; the 5-year survival rate is 6% [3]. The incidence of pancreatic cancer has increased during the past several decades and in 2014, an estimated 46,420 patients were diagnosed with pancreatic cancer and 39,590 died [3]. Pancreatic cancer is projected to surpass liver, breast, prostate, and colorectal cancers to become the second-leading cause of cancer-related death by 2030 [4].These statistics reflect the dire nature of the disease and lack of effective therapies. The location of the tumor results in few early symptoms and is often diagnosed at a late stage as a result. The absence of effective screening tools, and a limited understanding of risk factors, means that patients have advanced or metastatic disease at the time of diagnosis.

1.1.1 Pancreatic Cancer Treatment

Gemcitabine monotherapy was the major first-line metastatic pancreatic cancer treatment proven to prolong overall survival. Attempts to improve on gemcitabine single agent activity by combining it with other available chemotherapies have been largely unsuccessful [5],[6],[7]. During the last 5 years, two combination chemotherapy regimens emerged as new standards of care for first-line treatment of metastatic pancreatic cancer:

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

These demonstrate median overall survivals (OS) of 11.1 months and 8.5 months, respectively in separate Phase 3 studies [1], [2].

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 [7], [8].

Nal-IRI, a liposomal formulation of irinotecan, has recently been studied in a randomized, Phase 3, international study (NAPOLI-1), in which the combination of nal-IRI 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 [9].

The goal of the present study is to assess the safety, tolerability and preliminary efficacy of nal-IRI, in combination with 5-FU/LV and oxaliplatin in patients not previously treated for metastatic pancreatic adenocarcinoma. Descriptions of the approved anticancer therapies to be used in combination regimens on this study are briefly described below.

1.1.1.1 Description of 5-FU 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 DNA. It also interferes with 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 leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil 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 package insert for more details [10]).

1.2 Nal-IRI (MM-398)

Nal-IRI is irinotecan (also known as CPT-11) encapsulated in a nanoliposome drug delivery system (nanoliposomal irinotecan; nal-IRI). The active ingredient of the nal-IRI injection, irinotecan, is a member of the topoisomerase I inhibitor class of drugs and is a semi-synthetic and water soluble analog 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 [11], [12], [13]. Irinotecan is a pro-drug that is converted by nonspecific carboxylesterases into a 100-1000 fold more active metabolite, SN-38 [14]. 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 [15], [16].

Drug carrier technologies represent a rational strategy to improve the pharmacokinetics and biodistribution of irinotecan while protecting it from premature metabolism. Nal-IRI employs a novel intraliposomal drug stabilization 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 tumor 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 pharmacokinetics, high intravascular drug retention in the liposomes, and enhanced permeability and retention (EPR) effect may potentially result in site-specific drug delivery to solid tumors. Stromal targeting results from the subsequent depot effect, where liposomes accumulating in tumor associated macrophages (TAMs) release the active drug and convert it 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 neighboring cancer cells within the tumor.

1.2.1 Nal-IRI Pre-Clinical Experience

Nal-IRI has been shown in pre-clinical settings to have a broad spectrum of activity in a wide range of solid tumors 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-tumor activity against resistant or difficult to treat cancer models [17], [18], [19]. Nal-IRI has also shown potent antitumor activity, including durable tumor regressions, and was markedly superior to the equivalent dose of free drug in a bioluminescent-based orthotopic xenograft pancreatic model [20].

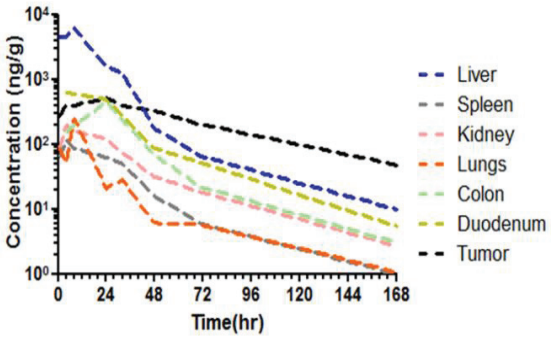
1.2.1.1 Nal-IRI Pre-Clinical Pharmacokinetics

The pharmacokinetic (PK) properties of nal-IRI were evaluated in an HT-29 colon cancer subcutaneous xenograft model, as reported by Kalra et al [19]. Both irinotecan and SN-38 were cleared very rapidly (within 8 hours) from the plasma following non-liposomal irinotecan administration; however, nal-IRI clearance was demonstrated to be considerably slower and remained in circulation for over 50 hours. SN-38 plasma exposure was also greater though C_{max} levels were reduced following nal-IRI 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 nal-IRI administration), yet there were relatively higher levels of prolonged accumulation in the tumor 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 tumoral accumulation when non-liposomal irinotecan is administered. In contrast, these data suggest that accumulation of nal-IRI in the tumor and subsequent liposome breakdown and local conversion of irinotecan to SN-38 is responsible for the enhanced tumor exposure of SN-38 when nal-IRI is administered. These preclinical data demonstrating longer retention time in tumor lesions with nal-IRI administration compared to non-liposomal irinotecan administration formed the basis for clinical development.

Figure 1: Tissue Distribution of nal-IRI in an HT-29 Xenograft Study.



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

1.2.2 Nal-IRI Clinical Experience

Nal-IRI has been studied in patients with solid tumors, including cervical cancer, gastric cancer, pancreatic cancer, and colorectal cancer. Disease areas currently being studied include glioma (intravenous and convection-enhanced local delivery), breast cancer and several pediatric solid tumors, including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, and osteosarcoma. Clinical studies of nal-IRI have been completed, with over 400 patients across multiple tumor types exposed to various dosing regimens, with additional studies actively recruiting patients across multiple tumor types (see Table 1 and Table 2).

Table 1: Summary of Completed Studies with Nal-IRI

Study	PEP0201	PEP0202	PEP0203	PEP0206	PEP0208	NAPOLI-1
Tumor Type	Solid tumors	Cervical	Solid Tumors	Gastric	Pancreas	Pancreas
Phase	1	1	1	2	2	3
Study design	Open label, dose escalation	Open label, dose escalation	Open label, dose escalation	Open label, 3 arm study comparing nal-IRI, docetaxel and irinotecan (44 patients/arm)	Open label, single arm	Randomized comparison of nal-IRI and nal-IRI+ 5-FU/LV *vs* a common control of 5-FU/LV
Number of Patients treated with nal-IRI	11	6	16	44	40	151 (monotherapy) 117 (combination)
Dosing Frequency	Q3W	Q3W	Q3W	Q3W	Q3W	Q3W (monotherapy) Q2W (combination)
Dose Level (mg/m^2)	60 (n = 1) 120 (n = 6) 180 (n = 4)	60 (n = 3) 80 (n = 3)	60 (n = 3) 80 (n = 6) 100 (n = 5) 120 (n = 2)	120	120	120 (monotherapy) 80 (combination)
Combination	No	Cisplatin	5FU/LV	No	No	5FU/LV
Combination dose	---	60 mg	2000/500 mg/m^2	---	---	2000/200 mg/m^2
Key result	MTD identified as 120 mg/m^2	Study terminated due to protocol violation	MTD identified as 80 mg/m^2	Similar safety profile across irinotecan and nal-IRI arms; 6 responses in nal-IRI arm met primary endpoint	Median survival of 5.2 months	Combination arm achieved median OS 6.1 months, 1.9-month improvement over control arm (HR=0.57; p-value=0.0009)

Date: 28 December 2016

Table 2: Summary of Open Studies with Nal-IRI

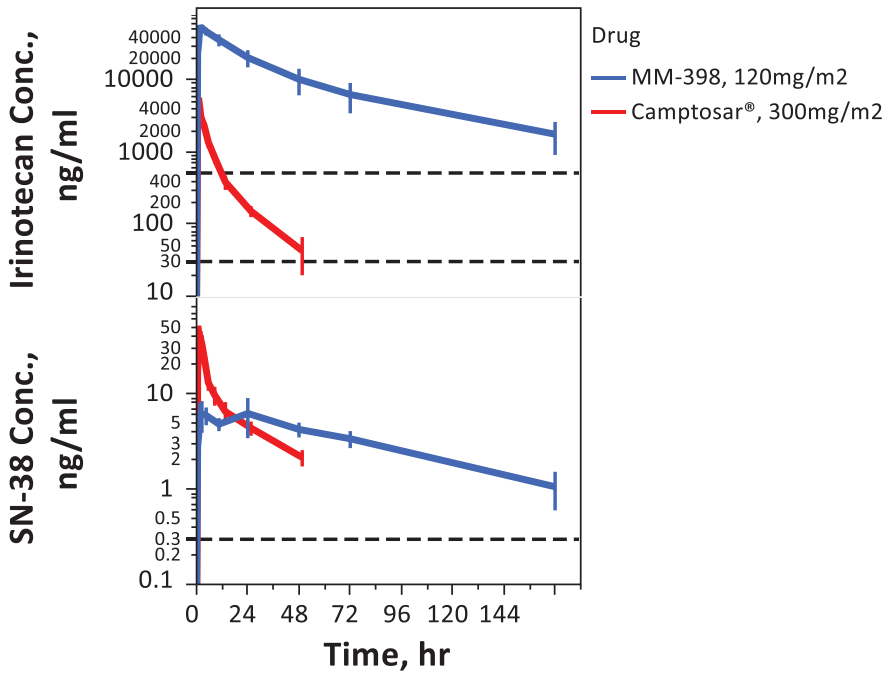
Study	UCSF 8603	PIST-CRC-01	PEPCOL	UCSF 13-12025		SPOC 2012-001	DOUBLIRI C13-4	MM-398-01-01-02
Tumor Type	Glioma	Colorectal	Colorectal	Glioma		Pediatric Solid Tumors	Colorectal	Breast
Phase	1	1	2	1		1	1	1
Study Design	Open label, dose escalation	Open label, dose escalation	Comparison of MM-398 + 5FU/LV + avastin versus FOLFIRI + avastin	Open label, dose escalation using convection-enhanced delivery for direct tumoral injection		Open label, dose escalation	Open label, dose escalation. MM-398 + irinotecan	Monotherapy with MM-398 evaluating Ferumoxytol MRI imaging feasibility
Dosing Frequency	Q3W	Q2W	Q2W	Single dose		Q3W	Q2W	Q2W
Dose Level (mg/m^2)	HTZ[a] 60 (n = 3) 90 (n = 5) WT[b] 120 (n = 6) 180 (n = 4) 240 (n = 3)	80 (n = 6) 90 (n = 6) 100 (n = 6)	80	Dose 20 mg 40 mg 60 mg 80 mg	Tumor Volume 1-4 cm^3 1-4 cm^3 2-5 cm^3 2-6 cm^3	60 (n = 1) 90 120 150 180 210	MM-398 60 (n = 3-6) 80 (n = 3-6)	80
Combination	No	No	5FU/LV	No		Cyclophosphamide	Irinotecan	No
Combination Dose	---	---	2400/400 mg/m^2 (5FU/LV) 5 mg/kg (avastin)	---		250 mg/m^2	90 or 120 mg/m^2 (Irinotecan)	---
Current Status	MTD identified for HTZ; escalation ongoing for WT	Enrollment completed in final cohort	Enrollment Completed	Enrollment ongoing		Enrollment ongoing	Enrollment completed. No MTD reached	Enrollment ongoing

[a] Heterozygous for UGT1A1*28
[b] Wildtype for UGT1A1*28
Date: 28 December 2016

1.2.2.1 Nal-IRI PK in Humans

The pharmacokinetic profile of single agent nal-IRI has been investigated in several studies, in which plasma levels of total irinotecan, SN-38 and encapsulated irinotecan were measured. In a single phase II clinical study (study PEP0206), direct comparison of the pharmacokinetics of irinotecan and SN-38 in patients administered nal-IRI or conventional (i.e. free) irinotecan (Camptosar®) was evaluated. Compared to the administration of conventional irinotecan 300 mg/m^2 q3w, administration of nal-IRI 120 mg/m^2 q3w resulted in higher exposure of total irinotecan (C_{max}: 13.4 fold, $AUC_{0-\infty}$: 46.2 fold, $t_{1/2}$: 2.0 fold), and higher SN-38 $t_{1/2}$ (3 fold) and marginally higher $AUC_{0-\infty}$ (1.4 fold), however, SN-38 C_{max} was reduced by 5.3 fold (Figure 2). In other PK studies of single agent nal-IRI, similar findings were observed when compared to standard doses of conventional irinotecan. Based on population pharmacokinetic analysis, no significant association was observed between the PK parameters of total irinotecan and SN-38 following nal-IRI monotherapy and when co-administered with 5-FU/LV. This result is consistent with the lack of drug interaction noted between irinotecan and 5-FU (Camptosar® US label). A summary table of PK parameters from 95 patients who received 60-180 mg/m^2 nal-IRI is found below (see Table 3). Please reference the Investigator Brochure for nal-IRI for additional information on pharmacokinetics.

Figure 2: Mean Plasma Concentrations of Total Irinotecan and SN-38 Following the Administration of Either MM-398 (120mg/m^2) or Camptosar® (300mg/m^2) in Study PEP0206



Gastric cancer patients received either nal-IRI (MM-398) at a dose of 120 mg/m^2 (blue line) or non-liposomal irinotecan (Camptosar®) at a dose of 300 mg/m^2 (red line) every 3 weeks. Total irinotecan (top) and its active metabolite, SN-38 (bottom) were measured during Cycle 1. Error bars indicate 95% confidence interval. Dotted lines indicate lower limit of quantification (LLOQ); total irinotecan measurements consist of two LLOQ values because of two different irinotecan assay was used to measure low and high range of concentrations. The concentrations less than LLOQ values were set to the corresponding LLOQ.

Table 3: Summary Statistics of nal-IRI PK Parameters across Multiple PK Studies

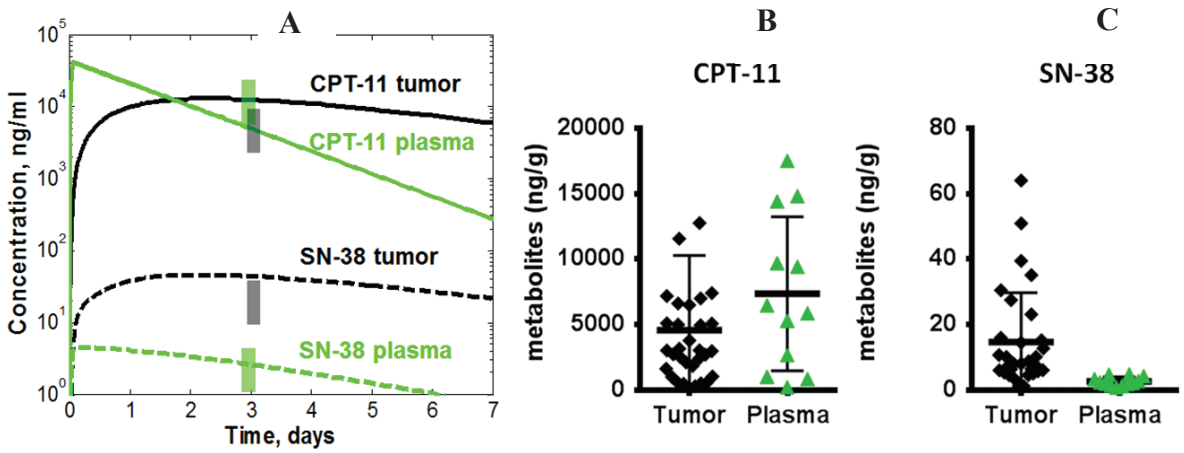
PK Parameters	Dose, mg/m^2	Analytes					
		Total Irinotecan			SN-38		
		N	Median	%IQR	N	Median	%IQR
C_{max} [µg/ml or ng/ml]‡	60	4	28.8	86	4	3.8	226
	80	25	38.0	36	25	4.7	89
	90	6	53.6	37	6	7.5	89
	100	11	41.9	25	11	6.2	79
	120	45	59.4	41	45	7.2	57
	180	4	102.4	32	4	11.8	89
$t_{1/2}$ [h]	60	4	22.0	87	3†	145.1	233
	80	23†	26.8	110	13†	49.3	103
	90	6	14.8	97	6	35.7	53
	100	11	21.6	192	10†	62.3	37
	120	45	15.6	198	40†	57.4	67
	180	4	22.8	86	4	50.2	122
$AUC_{0-\infty}$ [h·µg/ml or h·ng/ml]‡	60	4	352	489	3†	813	249
	80	23†	1030	169	13†	587	69
	90	6	1481	112	6	506	102
	100	11	919	256	10†	453	99
	120	45	1258	192	40†	574	64
	180	4	2076	90	4	1069	183
V_d [L/m^2]	60	4	3.0	87	NA	NA	NA
	80	23†	2.2	55	NA	NA	NA
	90	6	1.5	40	NA	NA	NA
	100	11	2.2	24	NA	NA	NA
	120	45	1.9	52	NA	NA	NA
	180	4	2.1	30	NA	NA	NA

† $t_{1/2}$ and $AUC_{0-\infty}$ were not calculated for a subset of patients due to insufficient number of samples in the terminal phase. NA= not available.

‡ C_{max} are in µg/ml for total irinotecan and ng/ml for SN-38; AUC are in h µg/ml for total irinotecan and h ng/ml for SN-38.

The above PK results obtained from patients treated with either nal-IRI or non-liposomal irinotecan confirmed the pre-clinical observation that nal-IRI extended plasma PK of both CPT-11 and SN-38 compared to treatment with non-liposomal irinotecan. Further, a Phase I clinical study of nal-IRI monotherapy (protocol nal-IRI-01-01-02; NCT# 01770353) investigated tumor levels of both CPT-11 and SN-38 following treatment with nal-IRI using post-treatment biopsies. Based on model predictions, SN-38 levels in tumor were expected to be higher than in plasma, suggesting local conversion of CPT-11 to SN-38 in the tumor microenvironment with nal-IRI (Figure 3A). Predictions were confirmed by measuring levels of CPT-11 and SN-38 in tumor biopsy samples collected from patients 72 hours post-dose, demonstrating 5-fold higher levels of SN-38 in the tumor than the plasma (Figure 3B-C). Collectively the evidence suggests that the prolonged systemic exposure to CPT-11 and SN-38 leads to prolonged levels of SN-38 in tumor tissue, which in turn leads to prolonged DNA damage to tumor cells, suggesting an advantage of nal-IRI compared to conventional irinotecan.

Figure 3: Clinical Evidence for Local Activation and Accumulation of SN-38 in Tumor Tissue



A) The mechanistic tumor PK model of nal-IRI predicted higher SN-38 levels in tumor compared to plasma. The range of actual data, collected from a Phase I study of patients (n=12) with advanced solid tumors, is indicated by the gray (tumor) or green (plasma) vertical bars.

B) CPT-11 levels

C) SN-38 levels, as measured from patient tumor (black) and plasma (green) samples collected 72h post-nal-IRI infusion.

1.2.2.2 Nal-IRI Safety in Humans

It has been shown in animal and human PK studies that once irinotecan is released from the nal-IRI liposomes, the conversion of irinotecan to SN-38 is similar to that of the unencapsulated irinotecan. The safety of nal-IRI, therefore, may be indirectly compared with the safety of irinotecan, primarily based on a qualitative comparison of adverse reactions, as reported in the Camptosar US label for irinotecan [21]. The comparison is qualitative, as both irinotecan and nal-IRI 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 nal-IRI 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, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, 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, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia (Camptosar US label).

With respect to irinotecan liposome, nal-IRI, when used in combination with 5-FU and leucovorin, the most common adverse reactions (≥20 %) observed in clinical trials considered to be related to are: diarrhea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anemia, stomatitis and pyrexia. The overall safety profile of nal-IRI is presented in detail in the related Investigator Brochure. Additionally, Table 4 summarizes ≥ Grade 3 safety data from the NAPOLI-1 trial comparing nal-IRI + 5-FU/LV (at a dose of 80 mg/m^2 given on an every 2 week schedule), or nal-IRI monotherapy (at a dose of 120 mg/m^2 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 patients who had received prior gemcitabine therapy.

Table 4: Summary of Grade 3 or Higher Adverse Events in NAPOLI-1 Study

	Nal-IRI + 5-FU/LV (N=117)	Nal-IRI (N=147)	5-FU/LV (N=134)
GRADE ≥3 NON-HEMATOLOGIC AEs IN >5% PATIENTS, %[a]			
Fatigue	14	6	4
Diarrhea	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 HEMATOLOGIC AES BASED ON LABORATORY VALUES, %[a, b]			
Neutrophil count decreased	20	16	2
Hemoglobin decreased	6	7	5
Platelet count decreased	2	1	0

[a] Per CTCAE Version 4
[b] Includes only patients who had at least one post-baseline assessment

1.2.2.3 Nal-IRI Clinical Efficacy in Pancreatic Cancer

Clinical efficacy of nal-IRI has been demonstrated in gemcitabine-refractory metastatic pancreatic cancer patients: in a randomized, Phase 3, international study (NAPOLI-1), nal-IRI was given as a monotherapy, or in combination with 5-FU/LV, compared to the control arm of 5-FU/LV alone. The majority of patients enrolled in this study had received prior chemotherapy in the metastatic setting (others received gemcitabine as neoadjuvant or adjuvant therapy). Approximately 1/2 of patients were categorized as second-line, and approximately 1/3 of patients were post-second line in the metastatic setting. The nal-IRI + 5-FU/LV combination significantly prolonged OS compared to 5-FU/LV treatment alone. The median OS for the nal-IRI + 5-FU/LV combination arm was 6.1 months compared to 4.2 months for the 5-FU/LV alone control arm with a stratified hazard ratio (HR) of 0.57 (95% CI: 0.41-0.80; p = 0.0009). The nal-IRI 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 nal-IRI alone. Further, in patients who received ≥80% of the protocol defined treatment during the first 6 weeks of treatment (the per protocol analysis), the nal-IRI + 5-FU/LV combination arm achieved a median OS of 8.9 months vs. 5.2 months for the control arm (HR 0.47 [95% CI 0.29-0.77]; p = 0.0018). The overall response rate in the nal-IRI + 5-FU/LV combination arm was 16% vs. 1% on the control arm (p <0.001) [22]. The results from this study are very promising and provide motivation for testing nal-IRI in pancreatic cancer patients not previously treated with gemcitabine.

1.3 Study Rationale

As mentioned previously, metastatic pancreatic cancer patients have a very poor prognosis and low median survival rates (< 1 year), necessitating the need for new treatment options. nal-IRI is a novel agent which has demonstrated efficacy in the Phase 3 NAPOLI-1 trial, in patients with metastatic pancreatic cancer who had progressed following gemcitabine-based therapy. This study will examine the safety, tolerability, and preliminary efficacy of nal-IRI in combination with 5-FU/LV and oxaliplatin in patients not previously treated for metastatic pancreatic adenocarcinoma.

1.3.1 Rationale for Nal-IRI + 5-FU/LV + Oxaliplatin

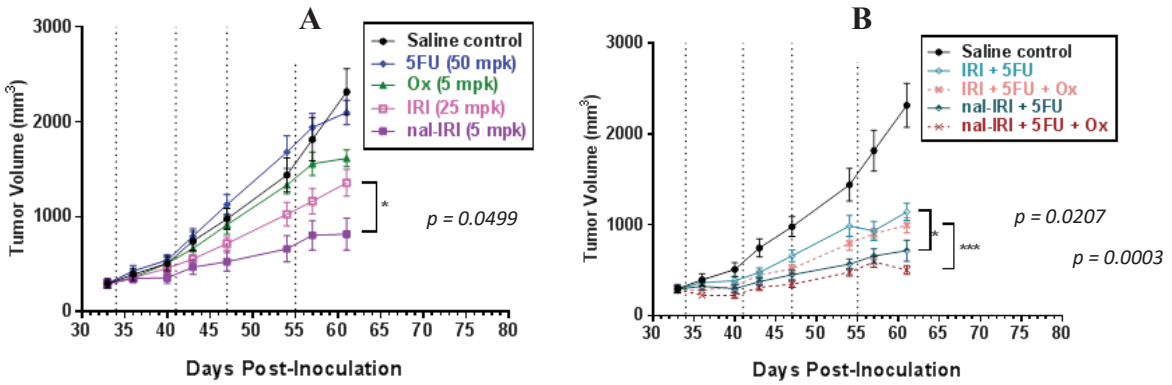
The combination of 5-FU/LV + irinotecan + oxaliplatin (the FOLFIRINOX regimen) has been studied in multiple clinical trials. As mentioned previously, FOLFIRINOX has become a standard of care regimen for patients with good performance status based on the results of a single Phase 3 trial conducted in France of 342 patients showing mOS of 11.1 months vs. 6.8 months for the gemcitabine alone control arm (HR 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001) [1]. The FOLFIRINOX regimen has been recommended by the NCCN as a preferred option for first-line metastatic disease since 2011 [23]. However, there are some concerns about the toxicity associated with FOLFIRINOX, as the reported incidence of grade 3 or 4 toxicity was significantly greater in the FOLFIRINOX group than in the gemcitabine control group, specifically neutropenia (46% vs. 21%), febrile neutropenia (5% vs. 1%), thrombocytopenia (9% vs. 4%), diarrhea (13% vs. 2%), and sensory neuropathy (9% vs. 0%) [1]. Concerns over toxicity have motivated attempts to modify the original FOLFIRINOX regimen, usually by omitting the 5-FU bolus component or reducing the dose of irinotecan, although it is currently unclear whether these modified approaches retain comparable efficacy [24].

In the current study, a modified FOLFIRINOX regimen will evaluate nal-IRI instead of conventional irinotecan, in order to improve the safety, tolerability, and ultimately efficacy of the original FOLFIRINOX regimen. With nal-IRI 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 2 study in colorectal cancer, data suggest that nal-IRI + 5-FU/LV may have less toxicity than FOLFIRI [25]. Therefore, toxicity of the nal-IRI-containing triplet regimen is not expected to be greater than that seen with FOLFIRINOX

By adding oxaliplatin to nal-IRI and 5-FU the potential to increase DNA damage and potentiate efficacy exists. Further, due to the nal-IRI prolonged PK properties and sustained tumor exposure, it is thought that using nal-IRI instead of conventional irinotecan would improve upon the efficacy of FOLFIRINOX. In order to test this hypothesis pre-clinically, the FOLFIRINOX regimen was tested against the nal-IRI + 5-FU/LV + oxaliplatin regimen in a pancreatic tumor xenograft mouse model (**Figure 4**). Results show that nal-IRI performed better than conventional irinotecan at equivalent exposure doses (5 mg/kg nal-IRI vs. 25 mg/kg free IRI) in the BxPC-3 pancreatic cancer model either alone (**Figure 4**A), or in combination with oxaliplatin and/or 5-FU (**Figure 4**B)

Cancer cells were implanted subcutaneously in mice; when tumors were well established and had reached mean volumes of ~300 mm3, IV treatment with non-liposomal irinotecan (IRI), nal-IRI, 5-FU, oxaliplatin (Ox) or control was initiated. Doses are indicated above for each treatment, and were given weekly x4 weeks, at time points indicated by dashed lines on graphs.

Figure 4: Efficacy of Nal-IRI in a 5-FU Insensitive Pancreatic Cancer Model (BxPC-3)



A) Single agent results of the individual treatments are shown, demonstrating nal-IRI significant inhibits tumor growth compared to free IRI.

B) Doublet or triplet regimens containing either IRI or nal-IRI in combination with oxaliplatin and/or 5-FU demonstrate that the nal-IRI-containing doublet and triplet inhibit tumor growth significantly better than the IRI-containing regimens.

In the mouse model tested, the addition of oxaliplatin to the doublet combinations of FOLFIRI or nal-IRI+5-FU/LV causes a slight increase in tumor growth inhibition (Figure 4B: compare light green to pink for FOLFIRI vs. FOLFIRINOX; compare dark green to red for nal-IRI+5-FU/LV vs. nal-IRI+5-FU/LV+Ox). However, comparison of FOLFIRI versus the nal-IRI+5-FU/LV doublet (light green vs. dark green), and FOLFIRINOX vs. the nal-IRI+5-FU/LV+Ox triplet (pink vs. red), demonstrates significantly more tumor growth inhibition with the nal-IRI-containing regimens. Further, the nal-IRI-containing doublet regimen performed better than the FOLFIRINOX triplet (dark green vs. pink), owing to the improved efficacy of nal-IRI compared to conventional irinotecan.

In humans, the standard dose regimen of FOLFIRINOX which demonstrated efficacy is 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, and fluorouracil at a dose of 400 mg/m^2 administered by IV bolus followed by a continuous infusion of 2400 mg/m^2. 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 [26] [8]. In the current study, a modified triplet regimen is proposed, whereby no bolus of 5-FU will be administered. The doses of oxaliplatin and nal-IRI determined from the combination regimens will be combined with the standard continuous infusion dose of 5-FU (excluding the bolus)/LV. Based on current clinical experience with nal-IRI in pancreatic cancer and the pre-clinical considerations outlined above, it is considered that the combination of nal-IRI and oxaliplatin with infusional 5-FU represents a novel therapeutic approach with the possibility of providing superior efficacy and tolerability over established FOLFIRINOX regimens.

*1.3.2 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. UGT1A1*28 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 Camptosar® (nonliposomal irinotecan). Multiple studies have evaluated the

association between UGT1A1*28 7/7 homozygosity, SN-38 concentration and safety in patients treated with Camptosar® 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 15-75 mg/m^2 daily for 5 days for 2 consecutive weeks (41-159% vs. 10-40%, respectively) [27] [28]. In a study of 66 patients who received single-agent non-liposomal irinotecan (350 mg/m^2 every 3 weeks), the incidence of Grade 4 neutropenia in patients heterozygous (UGT1A1*28 6/7) and homozygous (7/7) for the UGT1A1*28 was 12.5% and up to 50% respectively (Camptosar® USPI). In a subsequent study, association between UGT1A1*28 homozygosity and hematological toxicity was observed only in patients treated with >150 mg/m^2 non-liposomal irinotecan. By contrast, at lower dose of non-liposomal irinotecan (100-125 mg/m^2 every week) similar hematological toxicities were observed for both homozygous and non-homozygous patients [29]. 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 [30].

In patients treated with irinotecan liposome injection, the association between UGT1A1*28 homozygosity, SN-38, and hematologic toxicity is primarily obtained from study NAPOLI-1, where UGT1A1*28 homozygous patients were treated at reduced dose (50 vs 70 mg/m^2 every 2 weeks in combination with 5-FU/LV, or 70 vs. 100 mg/m^2 every 3 weeks monotherapy). The evaluation of the association between SN-38 concentration and UGT1A1*28 homozygosity was performed only for Caucasians, because homozygosity was rare in Asians (2/129; 1.5%). Based on the population PK and exposure-response analysis, similar un-encapsulated SN-38 C_{max} values were observed for homozygous and non-homozygous Caucasian patients if both are dosed at 70 mg/m^2 (1.99 [95% CI 1.81-2.18, n=12] and 1.76 [95% CI 1.69-1.84, n=141] ng/mL; p=0.66; both of these values are approximately half of the expected SN-38 C_{max} from a 120 mg/m^2 dose of non-liposomal irinotecan). Consequently, the predicted grade 3 or higher neutropenia was also similar if treated at 70 mg/m^2 monotherapy (8.7% vs. 7.4%, respectively), or if treated at 90 mg/m^2 monotherapy (15% vs. 13%, respectively). Additionally, in a phase I study (UCSF 8603), no differences in toxicity were seen in cohorts of UGT1A1*28 6/7 (n=18) or 6/6 (n=16) patients, 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 hematological toxicity appear to depend on the incoming load of SN-38 to be metabolized 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 patients 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) [31]. 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 US package insert 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 patients as a safety biomarker to further analyze the association between UGT1A1*228 homozygosity, SN-38 concentration and toxicity. Irinotecan liposome injection dose reduction will follow the same dose reduction rules for all patients regardless of UGT1A1*28 genotype. Patients with UGT1A1*28 homozygosity will be closely monitored for safety in comparison to the safety in patients with UGT1A1*28 non-homozygous status by the medical monitors of the sponsor and by the DLT committee.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the safety and tolerability of nal-IRI + 5FU/LV + oxaliplatin
- To characterize DLTs associated with nal-IRI + 5FU/LV + oxaliplatin and determine the recommended dose of the triplet combination for future development

2.2 Secondary Objectives

- To characterize the PK of nal-IRI in combination with 5-FU and oxaliplatin
- To evaluate efficacy signals with nal-IRI in combination with 5-FU/LV + oxaliplatin using overall response rate (ORR) [CR + PR, per RECIST v1.1], disease control rate (DCR) [CR + PR + SD, per RECIST v1.1], duration of response, PFS, and OS

2.3 Exploratory Objectives

- To evaluate the relationship between plasma PK of nal-IRI (total irinotecan, SN-38), in combination with 5-FU and oxaliplatin, and safety and efficacy endpoints in first-line metastatic pancreatic cancer
- To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI in combination with 5-FU/LV and oxaliplatin, PK, toxicity, and/or response

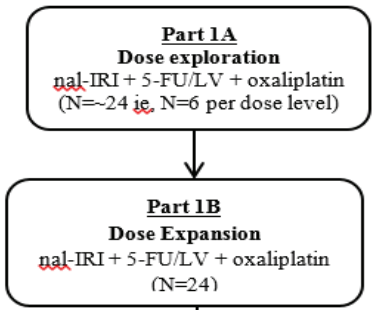
3 STUDY DESIGN

3.1 Study Design Overview

This is an open-label, phase 2 study to assess the safety, tolerability, and preliminary efficacy of nal-IRI in combination with 5-FU/LV and oxaliplatin in patients not previously treated for metastatic pancreatic adenocarcinoma.

The study will be conducted, as illustrated in the schematic below, with an initial dose exploration (Part 1A) followed by dose expansion (Part 1B) of the nal-IRI + 5-FU/LV + oxaliplatin regimen.

Figure 5: Overview of Study Design



In Part 1A safety and tolerability will be evaluated across a range of oxaliplatin and nal-IRI dose permutations, as summarized in Table 5. Oxaliplatin will be administered at intended dose levels of 60 mg/m^2 - 85 mg/m^2 IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. Nal-IRI will be administered at a dose range of 60 mg/m^2 – 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each cycle. 5-FU and leucovorin will be administered at fixed dose levels (2400 and 400 mg/m^2 respectively) for all dose level cohorts.

Part 1A will enroll cohorts of patients following a 3 + 3 dose escalation design, in order to select the dose level of the combination of oxaliplatin and nal-IRI to be used in Part 1B (dose expansion). Dose limiting toxicities, as defined in Section 3.2.2, will be assessed during the safety evaluation period (i.e. 28 days in Cycle 1; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to Section 6.5).

Safety evaluations are to be conducted regularly by the DLT committee to review all SAEs, AEs and DLTs for each patient to determine the safety and tolerability in each Cohort. The DLT Committee is comprised of the Investigators, the Medical Monitor, and the Sponsor.

In the absence of DLT, a minimum of 3 patients will be treated within each dose level cohort for a minimum of one cycle of therapy. Additional patients will be recruited into a cohort according to the DLT provisions outlined in Section 3.2.2, or if non-DLT toxicity is identified as requiring further evaluation by the DLT Committee.

In each dose level cohort, if there are no DLTs within the safety evaluation period, then additional dose level cohorts will be initiated following agreement by the DLT Committee. If one DLT occurs within the first 3 patients in a given dose level cohort, then the cohort will be expanded to a minimum of 6 patients. If 2 or more patients have DLTs within a given dose level cohort, that cohort will be considered to have not met the safety and tolerability criteria of the combination, and the cohort will stop.

As DLT within any cohort is potentially determined by a complex interaction between the respective dose levels of oxaliplatin and nal-IRI, the sequence of cohorts examined (dose levels -1 to -3) contains both dose escalation and dose de-escalation strategies for each individual drug, in order to control the total *combined* dose level within any given cohort. This means that for each individual drug, the dose level may decrease, increase or remain the same between successive cohorts.

The protocol Version 5.0 introduced a new dose level cohort in Part 1A (dose level -3: oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) to evaluate its safety and tolerability, following the completion of the dose level cohorts 1, -1 and -2B.

At the completion of the safety evaluation period (as defined in Section 3.2.2) for the last patient enrolled for dose level cohorts -1 to -3 (Part 1A) detailed in Table 5, all available data (DLT, SAE, and grade 3-4 adverse events, any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data) are reviewed by the DLT Committee. A dose level will be selected for expansion (for Part 1B as described below). The expansion cohort is intended to enroll 24 additional patients (total of 30 patients for the selected dose level) to obtain additional safety and efficacy data:

- If the dose level cohort -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) is considered to meet the safety and tolerability criteria, this dose will be selected for expansion.
- If the dose level cohort -3 is not considered to be safe and tolerable, the dose level cohort -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) will be selected for expansion.

No DLT assessment will be conducted for the expansion cohort.

Final determination of an appropriate combination regimen for potential future development will be made after all patients in the Part 1A (dose escalation) and Part 1B (expansion cohort) have completed two scheduled assessments (approximately 16 weeks of therapy; unless withdrawn at an earlier time point due to disease progression or drug-related toxicity) and will take into account all available data from the expansion cohort and also all available updated data for patients still receiving ongoing therapy in the other dose level cohorts. Data will include DLT, SAE, and grade 3-4 adverse events along with any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data.

Efficacy analysis will be performed when Week 16 DCR classifications can be made for all patients. This should occur when all patients have either achieved disease control at 16 weeks (i.e. have no PD up to and including the Week 16 assessment with documented non-PD [SD, PR, or CR] assessment) or have discontinued from treatment (refer to Section 5.3 for study treatment discontinuation criteria). Further details on DCR analyses are presented in Section 10.6.

Translational Research:

Translational research components will include collection of blood samples and archived tumor (during screening, if available) to look for potential biomarkers. Analyses may include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), or enzyme levels (e.g. MMP9).

3.2 Safety Assessment

3.2.1 Overview

Since the individual therapies included in the proposed combination have been studied in previous clinical trials, it is important that the safety assessment takes into account the expected safety profile of the standard dose regimen (e.g. FOLFIRINOX). The following adverse events are common (≥ 40%) with oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the nal-IRI-containing combination regimen: peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increases in transaminases and alkaline phosphatase, diarrhea, fatigue, emesis, and stomatitis. Additional adverse events may be

anticipated, as described in the package insert for oxaliplatin [10], including allergic and anaphylactic reactions. In a Phase 3 study of the FOLFIRINOX combination, the most common (> 5%) Grade 3-4 adverse events were: neutropenia, fatigue, vomiting, diarrhea, thrombocytopenia, sensory neuropathy, anemia, elevated alanine aminotransferase (ALT) level, thromboembolism, and febrile neutropenia [1].

3.2.2 DLT Definition (Nal-IRI + 5-FU/LV + Oxaliplatin)

For nal-IRI administered in combination with 5-FU/LV and oxaliplatin, the following adverse events will be considered as dose limiting toxicities (DLTs) if they occur during the safety evaluation period (i.e. 28 days of Cycle 1; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to Section 6.5) and are deemed related to the study treatment regimen.

- Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal therapy (withholding study drug and administering concomitant medication, e.g. G-CSF administration for neutropenia)
- Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection
- Any study regimen related adverse event that leads to a delay of the next scheduled study treatment dose for more than 14 days
- Any grade 4 non-hematologic toxicity with the specific *exclusion* of:
  - Fatigue/asthenia < 2 weeks in duration
  - Increases in alkaline phosphatase levels
  - Nausea and vomiting ≤3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen)
  - Diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)

Any adverse event that is related to disease progression will not be considered a DLT.

To be DLT evaluable, a patient should have received both doses of study medication at Cycle 1. A delay of up to 14 additional days (a total of 28 days) is permitted between the scheduled Day 1 and Day 15 administrations due to non-DLT drug related toxicity. Please see Section 4.2 for the guidance of patient replacement (dose level cohorts -1 to -3).

The final determination of DLTs will be made following discussion by the DLT Committee.

All patients will continue to be monitored for safety beyond Cycle 1, in order to determine if multiple cycles of treatment are tolerable.

If any patient within a given cohort experiences a DLT in Part 1A, they may continue in the study at a lower dose level of oxaliplatin and/or nal-IRI, (as determined by the DLT Committee in accordance with Section 6.5) upon resolution of the relevant toxicity. Other patients in the same cohort who do not experience a DLT will continue with unmodified dose levels of oxaliplatin and/or irinotecan (unless a dose modification is judged to be necessary by the DLT Committee on safety grounds).

4 ENROLLMENT AND TREATMENT

Approximately 54 patients will be enrolled in the study. All patients will be treated until disease progression (as determined by RECIST v1.1 criteria evaluated every 8 weeks from first dose of

study drug), unacceptable drug related toxicity, or physician or patient's choice (see Section 5.3).

It is expected that multiple sites will participate in this trial. Enrollment will be based on the availability of patients at each site and the availability of slots in each cohort. Slots must be confirmed by the Sponsor, or designee, prior to consenting patients to the study. A reasonable attempt will be made to equally distribute patients between sites. Enrollment can proceed to the next cohort after the safety data from the safety evaluation period in the previous cohort have been evaluated in accordance with Sections 4.1.1 and 4.1.2.

4.1 Dose levels

In each dose level cohort, if there are no DLTs within the safety evaluation period, then additional dose level cohorts will be initiated following agreement by the DLT Committee. If one DLT occurs within the first 3 patients in a given dose level cohort, then the cohort will be expanded to a minimum of 6 patients. If 2 or more patients have DLTs within a given dose level cohort, that cohort will be considered to have not met the safety and tolerability criteria of the combination, and the cohort will stop.

As DLT within any cohort is potentially determined by a complex interaction between the respective dose levels of oxaliplatin and nal-IRI, the sequence of cohorts examined (dose levels -1 to -3) contains both dose escalation and dose de-escalation strategies for each individual drug, in order to control the total combined dose level within any given cohort. This means that for each individual drug, the dose level may decrease, increase or remain the same between successive cohorts.

Planned dose evaluation is outlined in Table 5; additional details on dose administration are described in Section 6.

Any decisions by the DLT Committee to enroll additional dose level cohorts must be made according to the established decision process for cohort progression, as described in Section 4.1.1.

Table 5: Dose Escalation Table (Nal-IRI + 5-FU/LV + Oxaliplatin)

Evaluation Status	Dose Level	Oxaliplatin		5-FU/LV		Nal-IRI	
		Dose (mg/m^2)	Dose Day[a]	Dose (mg/m^2)	Dose Day[a]	Dose (mg/m^2)[b]	Dose Day[a]
Evaluation complete	1	60	1, 15	2400/400	1, 15	80	1, 15
Evaluation complete	-1	60	1, 15	2400/400	1, 15	60	1, 15
Not to be evaluated	CCI						
Not to be evaluated							
Evaluation complete	-2B	85	1, 15	2400/400	1, 15	60	1, 15
New dose level to be evaluated	-3	70	1, 15	2400/400	1, 15	65	1, 15

[a] Day indicated is part of a 28-day cycle
[b] Nal-IRI the dose is calculated in salt base.
Note: The dose of nal-IRI and 5-FU/LV in Dose Level 1 and 2 above is the same dose and schedule that was previously used in the NAPOLI-1 Phase 3 study.

The original plan in the study was to evaluate dose levels as described in the Table 5. Dose level cohorts 1, -1 and -2B have been evaluated. Dose levels 1 and -2B were considered to be not tolerable. Dose level -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable. Following the completion of the three predefined dose level cohorts, a new dose level -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) was introduced following a protocol

amendment (protocol Version 5.0) to evaluate its safety and tolerability. Dose levels 2 and -2A were considered not to be evaluated in the study. Prior to this Version 5.0, the enrollment of dose level cohorts 1, -1 and 2B had been completed.

4.1.1 Decision Process for Cohort Progression

Decisions to progress to the next dose level cohort will be made by mutual agreement of the DLT Committee (in accordance with the criteria described below (Section 4.1.2)). Regularly scheduled teleconferences of the DLT Committee will serve as a forum for ongoing review of safety and other relevant data. Decisions to progress to the next dose level cohort must be agreed by the majority of the DLT Committee members, and will be documented along with a summary of the information supporting the decision.

4.1.2 Decision Criteria for Cohort Progression

The safety assessment period for purposes of DLT evaluation and dose level cohort progression decisions will be one cycle of treatment (i.e. 28 days of Cycle 1; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to Section 6.5). Progression to the next dose level cohort will only occur after all available safety and other relevant data have been evaluated for the current dose level cohort (once the last patient enrolled in the cohort completes the safety evaluation period). Potential data which may be reviewed by the DLT Committee for the purposes of dose level assessment include DLT, SAE, and grade 3-4 adverse events, any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data.

In addition, any drug-related toxicities of Grade 3 or higher occurring after Cycle 1 of each cohort will be assessed by the DLT Committee on an ongoing basis for their potential relationship to cumulative toxicity of one or more study agents and will be considered as appropriate in decisions to progress to subsequent dose level cohorts.

4.2 Patient Replacement

For Part 1A (dose level cohorts -1 to -3), any patient requiring a dose delay of >14 days during the safety evaluation period due to non-drug related reasons will be replaced for DLT evaluation purposes. Any patient not receiving both doses of study drug during the safety evaluation period, for reasons other than dose limiting toxicity, will be replaced for DLT evaluation purposes.

For Part 1B (the expansion period), patients withdrawing from treatment with study medication will **not** be replaced.

5 PATIENT SELECTION AND DISCONTINUATION

5.1 Inclusion Criteria

In order for inclusion into the study, patients must have/be:

(a) Histologically or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to Screening

(b) At least one tumor lesion measurable by CT or MRI scan (according to RECIST v1.1 criteria)

(c) ECOG performance status of 0 or 1 at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening. Two observers will be required to assess ECOG. If different, the lowest assessment will be used for the eligibility evaluation at each assessment (criterion applicable only for Part 1A)

(d) Adequate biological parameters as evidenced by all of the following blood counts:
- Absolute neutrophil count (ANC) > 1,500 cells/µl without the use of hematopoietic growth factors within last 7 days prior to Screening
- Platelet count > 100,000 cells/µl
- Hemoglobin > 9 g/dL; transfusion is allowed, provided interval is ≥ 7 days prior to Screening

(e) Adequate hepatic function as evidenced by:
- Serum total bilirubin ≤ ULN (biliary drainage is allowed for biliary obstruction), and
- AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present)

(f) Adequate renal function as evidenced by serum creatinine ≤ 1.5 x ULN, and calculated clearance ≥60 mL/min/1.73 m^2 for patients with serum creatinine levels above or below the institutional normal value. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); for patients with body mass index (BMI) >30 kg/m^2, lean body weight should be used instead.

(g) ECG without any clinically significant findings (e.g. QTc ≤450 ms for males and ≤470 ms for females and no known arrhythmias)

(h) Recovered from the effects of any prior surgery or radiotherapy

(i) ≥ 18 years of age

(j) Inclusion criteria removed (protocol Version 5.0)

(k) Able to understand and provide an informed consent

(l) Patient has a Karnofsky performance status (KPS) ≥ 70 at Screening, and within 72 hours prior to date of first dose if first dose occurs more than 72 hours after screening. Two observers will be required to assess KPS. If discrepant, the one with the lowest assessment will be considered true (criterion applicable only for Part 1B, added in protocol Version 6.0)

5.2 Exclusion Criteria

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

(a) Prior treatment of pancreatic cancer in the metastatic setting (or locally advanced setting) with surgery, radiotherapy, chemotherapy or investigational therapy (Note: palliative radiotherapy is permitted; placement of biliary stent is allowed)

(b) 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 (modified in protocol Version 6.0)

(c) Uncontrolled CNS metastases (Note: Patients who require steroids should be on a stable or decreasing dose to be eligible)

(d) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, diarrhea > grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction

(e) History of any second malignancy in the last 3 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of

other malignancies are eligible if they have been continuously disease free for at least 3 years.

(f) Known hypersensitivity to any of the components of nal-IRI, other liposomal products, or any components of 5-FU, leucovorin or oxaliplatin

(g) Exclusion Criteria removed (protocol Version 6.0)

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

- Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion
- NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure
- Known historical or active infection with HIV, hepatitis B, or hepatitis C

(i) 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, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome

(j) Use of strong CYP3A4 inhibitors or inducers, or strong UGT1A1 inhibitors (patients are ineligible if unable to discontinue the use of strong CYP3A4 or UGT1A1 inhibitors at least 1 week or strong CYP3A4 inducers at least 2 weeks prior to receiving first dose of irinotecan liposome injection), or presence of any other contraindications for irinotecan[1]

(k) Presence of any contraindications for nal-IRI, 5-FU, leucovorin, or oxaliplatin

(l) Exclusion Criteria removed (protocol Version 6.0)

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

(n) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy within 7 days prior to the first dose based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 6 months following the last dose of study drug.[2]

(o) Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma

(p) Documented serum albumin <3 g/dL at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening (both labs at screening and prior to first dose may be confirmed locally)

(q) Patients 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

(r) Previous treatment with irinotecan-based, nab-paclitaxel-based or gemcitabine-based resulting in disease progression (added in protocol Version 6.0)

[1] See Section 6.8 for examples of strong CYP3A4 or UGT1A1 inhibitors or CYP3A4 inducers.

[2] For a description of highly effective contraceptive measures, please see Appendix 1.

5.3 Patient Discontinuation

5.3.1 Discontinuation of Study Treatment

It is intended that patients will be treated until radiologically determined progressive disease per RECIST v1.1 or unacceptable study drug related toxicity. However, a patient 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 v1.1
- Clinical deterioration sufficient to prevent further radiological assessment
- A study drug related adverse event, prior to disease progression, which:
  - in the opinion of the Investigator, precludes further treatment with all study drugs
  - requires treatment with one or more study drugs to be withheld for more than 14 days, unless in the opinion of the investigator the patient is receiving benefit overall from the study treatment
  - would result in a fourth dose reduction in any single study drug (in a patient having already experienced 3 previous dose reductions)
  - requires discontinuation of nal-IRI
- Development of an intercurrent medical condition or need for concomitant therapy that precludes further treatment with all study drugs
- Withdrawal of consent for further treatment
- Pregnancy

A patient who discontinues study medication and has **not** withdrawn from the study must continue with all ongoing protocol requirements, as detailed in Section 5.3.3.

5.3.2 Withdrawal from the Study

A patient may withdraw, or be withdrawn, from the study at any time. Reasons for withdrawal from the study include, but are not limited to the following:

- Significant noncompliance with the protocol, per Investigator's assessment
- The Investigator removes the patient from the trial in the best interests of the patient
- Use of prohibited concomitant medications
- Patient is lost to follow up
- Withdrawal of consent for further participation in the study
- Death
- Study termination by the Sponsor

5.3.3 Procedures following Study Drug Discontinuation or Study Withdrawal

Following **study drug discontinuation** all procedures and evaluations required at the 30-day (End of Treatment) follow up visit should be completed. All patients who discontinue study medication as a result of an adverse event must be followed until resolution or stabilization of the adverse event. Patients who discontinue study drug 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 v1.1 has been documented. Overall survival follow-up contacts should continue every 2 months from the 30-day follow-up visit until death or study closure, whichever comes first. If a patient does not return to the clinic for follow-up visits, attempts should be made to contact the patient via phone, email, or mail. At least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient is considered lost to follow-up, the date of death may be captured from public records.

If a patient **withdraws from the study** at any point, a complete final evaluation at the time of the patient'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 patient whether they still consent to be followed up for survival status only (including where**

appropriate through publicly available records) and any such consent to ongoing survival follow up must be documented in both the source hospital records and the eCRF.

6 STUDY TREATMENT

6.1 Investigational Product

6.1.1 Description of Nal-IRI (MM-398)

Nal-IRI (irinotecan liposome injection, also known MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. It will be supplied in sterile, single-use vials containing 10 mL of nal-IRI at a concentration of 5 mg/mL. nal-IRI must be stored refrigerated at 2 to 8°C, with protection from light (do not freeze). The appearance of nal-IRI is white to slightly yellow opaque liquid.

6.1.1.1 Storage and Handling of Nal-IRI (MM-398)

Nal-IRI must be stored refrigerated at 2 to 8 °C, with protection from light. Nal-IRI 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 drug.

Nal-IRI must be diluted prior to administration. The diluted solution is physically and chemically stable for 4 hours at room temperature (15 – 25 °C), but it is preferred to be stored at refrigerated temperatures (2 – 8 °C). The diluted solution must not be frozen, and must be protected from light until infusion. Because of possible microbial contamination during dilution, the diluted solution should be administered within 24 hours of preparation if refrigerated (2 – 8 °C), and within 4 hours if kept at room temperature (15 – 25 °C).

6.1.1.2 Packaging and Labeling of Nal-IRI (MM-398)

Nal-IRI will be packaged in a multi-vial cardboard carton. The individual vials, as well as the outside of the cardboard carton, will be labeled in accordance with local regulatory requirements.

6.1.1.3 Administration of Nal-IRI (MM-398)

See combination regimen administration instructions below in Section 6.3.2.

6.1.1.4 Potential Toxicity of Nal-IRI (MM-398)

Data from previous nal-IRI studies does not show any unexpected toxicity when compared to the active ingredient, irinotecan, which has been studied extensively. The warnings and precautions for the use of irinotecan and the recommended treatment procedures for managing those toxicities are provided below. Certain known adverse reactions of irinotecan have not been observed with nal-IRI to date. This could be due to the limited cumulative patient exposure to date of nal-IRI, or the use of appropriate premedication and early recognition and treatment of expected adverse events. The adverse reactions not observed include anaphylaxis or anaphylactoid reaction, interstitial lung disease-like pulmonary toxicity and acute pancreatitis. There is insufficient evidence to know whether these known adverse reactions of irinotecan are also associated with nal-IRI.

Diarrhea

Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. For patients who

experienced early cholinergic symptoms during the previous cycle of nal-IRI, prophylactic administration of atropine will be given at the discretion of the investigator.

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide, and octreotide should be considered if diarrhea persists after loperamide, as described in Section 6.7.2 (Therapy for Diarrhea). Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan and nal-IRI. In patients with metastatic pancreatic cancer in the NAPOLI-1 study receiving irinotecan liposome injection/5-FU/LV, the incidence of grade 3 or 4 neutropenia was higher among Asian patients (18 of 33 [55%]) compared to White patients (13 of 73 [18%]). Neutropenic complications should be managed promptly with antibiotic support. Granulocyte-colony stimulating factor (G-CSF) may be used to manage neutropenia at the investigator's discretion. Prophylactic use of Granulocyte-colony stimulating factor (G-CSF) will be permitted if patients are considered high risk in the opinion of the investigator as specified in Section 6.7.1.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed with irinotecan, however, have not been observed with nal-IRI to date. This could be due to the limited cumulative patient exposure to date of nal-IRI, or the use of appropriate premedication and early recognition and treatment of expected adverse events. There is insufficient evidence to know whether these known adverse reactions of irinotecan are also associated with nal-IRI. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions occur.

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support.

Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan-containing regimens; the specific cause of these events has not been determined.

Pregnancy

The pregnancy category of irinotecan is D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan. If a pregnancy is reported, treatment should be discontinued. The patient should be withdrawn from the study, and the pregnancy should be followed until the outcome becomes known.

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.

Patients at Particular Risk

In clinical trials of the weekly schedule of irinotecan, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p < 0.001$). Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan.

Acute Infusion Associated Reactions

Acute infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications. See Section 6.4 for guidelines on the management of infusion reactions.

Other Potential Toxicities

Nal-IRI, the liposomal formulation of irinotecan is different from irinotecan in unencapsulated formulation, so there is a potential for toxicities other than those caused by irinotecan. All patients should be monitored closely for signs and symptoms indicative of drug toxicity, particularly during the initial administration of treatment.

6.2 Additional Anticancer Therapies

Patients will be treated with one or more of the following approved therapies:

- 5-FU/LV
- oxaliplatin

6.2.1 Description of Combination Therapies

A description of each anticancer therapy to be used in combination with nal-IRI is described in Section 1.1.1. Please also refer to the package inserts [10], [32], or Summary of Product Characteristics (SmPC) for sites located in the European Union (EU), for more details.

6.2.2 Storage and Handling of Combination Therapies

Refer to the country specific package inserts or SmPC for details on storage and handling for 5-FU and leucovorin and oxaliplatin.

6.2.3 Packaging and Labeling of Combination Therapies

Sites participating in this protocol will source their own combination therapy supplies. However, for sites where this is not possible due to country legal or regulatory restrictions, Ipsen will provide commercially available 5-FU, leucovorin and oxaliplatin as required by their enrolled patients for their specific treatment regimen.

Ipsen sourced combination therapy supplies will be labeled in accordance with local regulatory requirements, and site accountability for all Ipsen sourced clinical trial material is required and will be monitored by the sponsor or its representatives.

6.2.4 Potential Toxicities of Combination Therapies

6.2.4.1 Potential Toxicities with 5-FU

Stomatitis and esophago-pharyngitis (which may lead to sloughing and ulceration), diarrhea, 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 US package insert or SmPC). Common adverse events (≥20 %) that were observed with nal-IRI in combination with 5-FU/LV in clinical trials considered to be related were: diarrhea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anemia, stomatitis and pyrexia.

6.2.4.2 Potential Toxicities with Oxaliplatin

The following adverse events are relatively common (≥ 40%) with oxaliplatin treatment in combination with 5-FU/LV and are to be expected with the nal-IRI-containing regimen: peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increases in transaminases and alkaline phosphatase, diarrhea, fatigue, emesis, and stomatitis. In a phase 3 study of the FOLFIRINOX regimen (5-FU/LV + irinotecan + oxaliplatin), the most common (> 5%) Grade 3-4 adverse events were: neutropenia, fatigue, vomiting, diarrhea, thrombocytopenia, sensory neuropathy, anemia, elevated alanine aminotransferase (ALT) level, thromboembolism, and febrile neutropenia [1]. Grade 3/4 hypersensitivity reactions, including anaphylactic reactions, have been observed in 2-3% of colon cancer patients receiving oxaliplatin; see package insert for more information. See Section 6.4 for guidelines on the management of infusion reactions. Additional adverse events may be anticipated, as described in the package insert or SmPC for oxaliplatin [10].

6.3 Combination Regimen Dosage and Administration

6.3.1 Nal-IRI + 5-FU/LV + Oxaliplatin

The order of the infusions to be administered in the clinic will be as follows: nal-IRI will be administered first, followed by oxaliplatin, then LV, followed by 5-FU.

Patients will receive the oxaliplatin infusion 2 hours after the completion of the nal-IRI infusion and will receive leucovorin 30 min after oxaliplatin.

6.3.1.1 Premedication

All patients must be premedicated prior to nal-IRI infusion, 5-FU/LV infusion, and oxaliplatin infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics according to standard institutional practices for irinotecan, 5-FU, and oxaliplatin administration, or the Summary of Product Characteristics (SmPC) for sites located in the European Union (EU). In situations where differences in standard institutional practices and recommendations within the country relevant SmPC occur, standard institutional practice will take precedence. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles.

6.3.2 Doses and Administration of Nal-IRI

Nal-IRI will be administered at doses of 60 mg/m^2 to 80 mg/m^2 (as outlined in Section 4.1).

Nal-IRI will be administered as an IV infusion over 90 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days.

Prior to administration, the appropriate dose of nal-IRI must be diluted in 5% Dextrose Injection (D5W) or 0.9% Sodium Chloride Injection to a final volume of 500 mL. Care should be taken not to use any diluents other than D5W or 0.9% sodium chloride.

The actual dose of nal-IRI to be administered will be determined by calculating the patient's body surface area at the beginning of each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since nal-IRI vials are single-use vials, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

6.3.3 Doses and Administration of 5-FU and Leucovorin

- Leucovorin will be administered at a dose of 400 mg/m^2 of the l + d racemic form, or l form 200 mg/m^2, as an IV infusion over 30 minutes (±5 minutes), on Days 1 and 15 of each 28-day cycle
- 5-FU will be administered at a dose of 2400 mg/m^2 as an IV infusion over 46-hours (±60 minutes), on Days 1 and 15 of each 28-day cycle

Leucovorin should be reconstituted per the instructions on the package insert, SmPC or standard institutional guidelines for reconstitution of leucovorin.

Leucovorin should be administered prior to the 5-FU infusion. Actual dose of 5-FU and leucovorin to be administered will be determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.

6.3.4 Doses and Administration of Oxaliplatin

Oxaliplatin will be administered at varying dose levels as indicated in Table 5 (from 60 mg/m^2 - 85 mg/m^2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle

Oxaliplatin should be prepared according to the instructions on the package insert, SmPC or per standard institutional guidelines for preparation and administration of oxaliplatin. In situations where differences in standard institutional practices and recommendations within the country relevant SmPC occur, standard institutional practice will take precedence.

Oxaliplatin should be administered following nal-IRI infusion; the first 3 patients in Dose Level 1 will begin the oxaliplatin infusion two hours after the completion of the nal-IRI infusion (see Section 6.3.1). Actual dose of oxaliplatin to be administered will be determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.

6.4 Management of Infusion Reactions

The guidelines described in this section can be followed in case of infusion reactions to any study treatment given per protocol (e.g. nal-IRI, oxaliplatin). Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.03) definitions of an allergic reaction or anaphylaxis as defined below:

Allergic reaction (i.e., a disorder characterized 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; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)

Grade 4: Life-threatening consequences; urgent intervention indicated

Anaphylaxis (i.e., a disorder characterized 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 edema/angioedema; hypotension

Grade 4: Life-threatening consequences; urgent intervention indicated

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

Grade 1

- Slow infusion rate by 50%
- Monitor patient every 15 minutes for worsening of condition
- Future infusions may be administered at a reduced rate (e.g. over 120 minutes for nal-IRI), at the discretion of the Investigator

Grade 2

- Stop infusion
- Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen
- Resume infusion at 50% of the prior rate once infusion reaction has resolved
- Monitor patient every 15 minutes for worsening of condition
- For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.
- Future infusions may be administered at a reduced rate (e.g. over 120 minutes for nal-IRI), at the discretion of the Investigator

Grade 3

- Stop infusion and disconnect infusion tubing from patient
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary
- No further treatment will be permitted

Grade 4

- Stop the infusion and disconnect infusion tubing from patient
- Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV and other medications as medically necessary
- Consider hospital admission for observation
- No further treatment will be permitted

For patients who experience a second grade 1 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally or as per institutional guidelines.

6.5 Dose Modifications

The toxicity of each cycle must be recorded prior to the administration of a subsequent cycle and graded according to the NCI CTCAE (Version 4.03). All dose reductions for all arms should be based on the worst preceding toxicity.

Dosing may be held 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. If the time required for recovery from toxicity is more than 14 days, consideration should be given to discontinuing the patient from further treatment, unless the patient 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. If oxaliplatin is not well tolerated, oxaliplatin may be discontinued and patients may continue to receive nal-IRI + 5-FU/LV at the discretion of the Investigator. Toxicity requiring discontinuation of nal-IRI will result in discontinuation from all study treatments.

If a patient's dose is reduced during the study due to toxicity, it should remain reduced for the duration of the study; dose re-escalation to an earlier dose is not permitted. Any patient who has 3 dose reductions and experiences an adverse event that would require a fourth dose reduction must be discontinued from study treatment.

Prior to each dosing, patients must have:

- ANC ≥ 1500/mm^3
- WBC ≥ 3500/mm^3
- Platelet count ≥ 100,000/mm^3
- Diarrhea ≤ Grade 1

Treatment should be delayed to allow sufficient time for recovery to levels noted above, and upon recovery, treatment should be administered according to the guidelines in the tables below. The use of transfusions and/or growth factor support is permitted if within normal institutional policies and procedures. If the patient had febrile neutropenia, the ANC must have resolved to ≥ 1500/mm3 and the patient must have recovered from infection. For Grade 3 or 4 non-hematological toxicities, treatment should be delayed until they resolve to Grade 1 or baseline. Guidelines for dose adjustments of each individual treatment within the regimen are found in the tables below for hematologic toxicities (Table 6), and for non-hematological toxicities (Table 8), and were based on published dose modifications for the established FOLFIRINOX regimen [1]. In case a patient experiences an infusion reaction, either institutional guidelines or the guidelines provided for infusion reaction management (see Section 6.4) should be followed.

For all tables below, patient should be withdrawn from study treatment if more than 3 dose reductions are required. No dose adjustments for toxicity are required for leucovorin. Leucovorin must be given immediately prior to each 5-FU dose; hence, if 5-FU dose is held, leucovorin dose should be held as well.

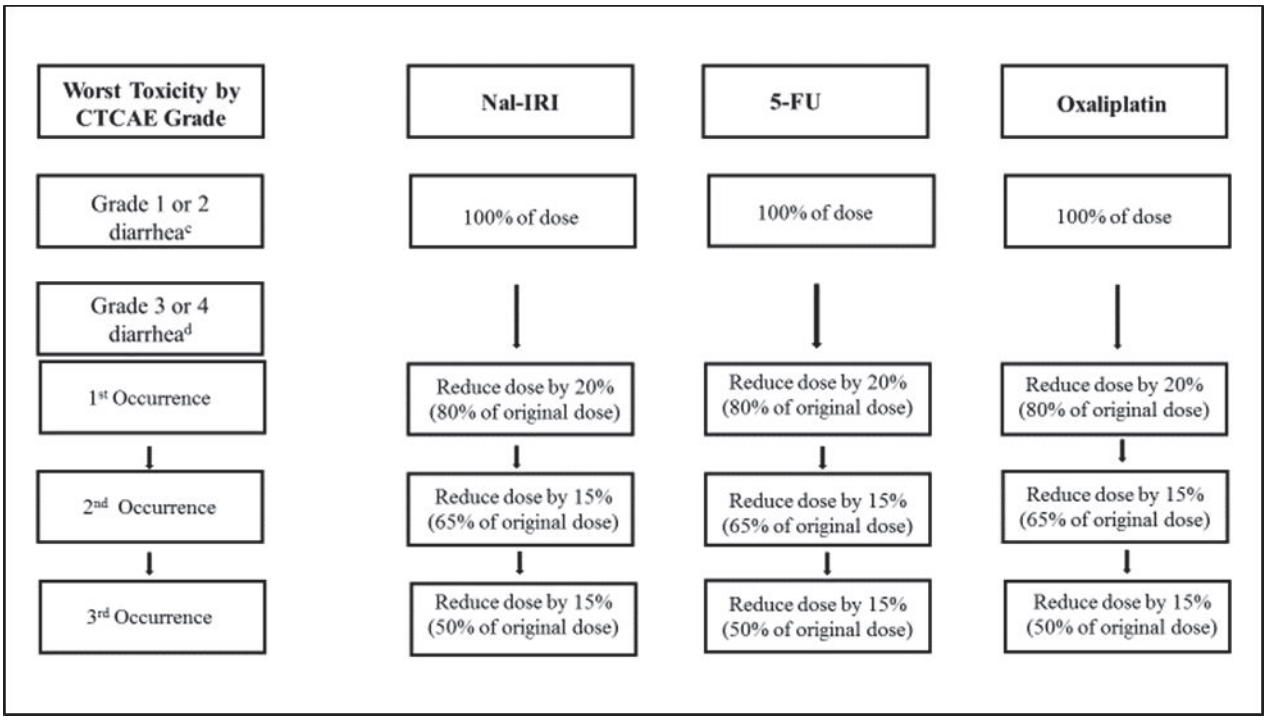
Toxicity that requires discontinuation from oxaliplatin only (e.g. neuropathy) will result in the option, at the discretion of the Investigator to continue on study treatment with nal-IRI + 5-FU/LV only for all future dosing. Toxicity requiring discontinuation of nal-IRI will result in discontinuation from all study treatment.

Table 6: Dose Modifications for Hematologic Toxicities[a,b,c,d]

Worst Toxicity by CTCAE Grade	Nal-IRI	5-FU	Oxaliplatin
Grade 2 hematotoxicity	100% of previous dose		
Grade 3- 4 neutropenia[e] (ANC ≤ 1000/mm^3) or febrile neutropenia and/or thrombocytopenia	1st occurrence: Reduce dose by 20% (80% of original dose) 2nd occurrence: Reduce dose by another 15% (65% of original dose) 3rd occurrence: Reduce dose by another 15% (50% of original dose)		
Other Grade 3 or 4 hematologic toxicities not specifically listed above	1st occurrence: Reduce dose by 20% (80% of original dose) 2nd occurrence: Reduce dose by another 15% (65% of original dose) 3rd occurrence: Reduce dose by another 15% (50% of original dose)		

[a] Any toxicity ≥ Grade 2 can justify a dose reduction if medically indicated following above guidance
[b] 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.
[c] Patients who require more than 3 dose reductions must discontinue study treatment.
[d] Prophylactic use of Granulocyte-colony stimulating factor (G-CSF) will be permitted if patients are considered high risk in the opinion of the investigator
[e] Consider the use of G-CSF for patients who experience ≥ Grade 3 neutropenia or febrile neutropenia

Table 7: Dose Modifications for Diarrhea[a,b]



[a] Any toxicity ≥Grade 2 can justify a dose reduction if medically indicated following above guidance
[b] Patients who require more than 3 dose reductions must discontinue study treatment
[c] Grade 1 diarrhea: 2-3 stools/day >pretreatment; Grade 2 diarrhea: 4-6 stools/day >pretreatment
[d] Grade 3 diarrhea: >9 stools/day >pretreatment; Grade 4 diarrhea: life threatening consequences
[e] Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms (acute diarrhea. and abdominal cramps during or within 24 hours after nal-IRI administration)

Table 8: Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia[a,b,e]

Worst Toxicity by CTCAE Grade	Nal-IRI	5-FU	Oxaliplatin
Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy AND 1st occurrence: Reduce dose by 20% (80% of original dose) 2nd occurrence: Reduce dose by another 15% (65% of original dose) 3rd occurrence: Reduce dose by another 15% (50% of original dose)		
Grade 2 hand foot syndrome	100% of previous dose[b]	1st occurrence: Reduce dose by 20% (80% of original dose) 2nd occurrence: Reduce dose by another 15% (65% of original dose) 3rd occurrence: Reduce dose by another 15% (50% of original dose)	100% of previous dose[b]
Grade 3 or 4 hand foot syndrome	100% of previous dose[b]	Discontinue therapy	100% of previous dose[b]
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	100% of previous dose[b]	Discontinue therapy	100% of previous dose[b]
Sensory neuropathy	100% of previous dose[b]	100% of previous dose[b]	Grade 2, persistent: Reduce dose by 20% (80% of original dose) Grade 3, recovers prior to next cycle: Reduce dose by 35% (65% of original dose) Grade 3, recurrent: Reduce dose by 15%[d] (50% of original dose) Grade 3 persistent or Grade 4: Discontinue therapy[c]
Grade 3 or 4 hepatic, renal, respiratory or other toxicities	1st occurrence: Reduce dose by 20% (80% of original dose) 2nd occurrence: Reduce dose by another 15% (65% of original dose) 3rd occurrence: Reduce dose by another 15% (50% of original dose)		

[a] Asthenia and Grade 3 Anorexia do not require dose modification
[b] Any toxicity ≥ Grade 2, except asthenia and alopecia, can justify a dose reduction if medically indicated
[c] Patients who discontinue therapy due to oxaliplatin-related neuropathy may remain on study and continue to receive nal-IRI + 5-FU/LV
[d] At the discretion of the investigator, patients can discontinue oxaliplatin therapy if Grade 3 persistent sensory neuropathy occurs.
[e] Patients who require more than 3 dose reductions must discontinue study treatment

*6.5.1 Nal-IRI Dose Modifications for UGT1A1*28 Positive Patients*

As part of this study, pharmacogenomic data will be collected on all patients for determination of UGT1A1*28 status.

Based on previous experience with 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 [25],

in a study of 66 patients who received single-agent irinotecan (350 mg/m^2 once every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was as high as 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%.

Importantly however, no grade 4 neutropenia was observed in patients homozygous for the wild-type (WT) 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 [25]). Population PK studies of nal-IRI have not identified a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure (see Investigator Brochure). In a Phase I study (UCSF 8603, as referenced in Table 2 above) no differences in toxicity were seen in cohorts of heterozygous or WT patients, and DLTs of diarrhea with or without accompanying dehydration or fatigue, were seen in both cohorts.

Because of these discrepancies in the severity of previously documented toxicity arising from UGT1A1*28 homozygosity, and because the prevalence of UGT1A1*28 homozygosity is relatively low, testing results will not be required prior to the first dose of nal-IRI on this study and the starting dose for all patients will be as described in Table 5.

The protocol does not contain formal recommendations on nal-IRI dose modifications as a consequence of homozygosity. All patients should receive the full starting dose of nal-IRI. The UGT1A1*28 status of each patient will subsequently be made available to individual investigators.

6.5.2 Other Toxicities Requiring Special Attention

QTc prolongation that occurs in the setting of diarrhea 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 diarrhea as described above.

6.5.3 Rules for Dose Omissions and Modified Schedules

The following guidance should be followed when all study drugs are held/missed:

The maximum delay between the date of a scheduled but missed dose and the planned next dose should be up to 14 days.

6.6 Drug Accountability

The Investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of all study drugs provided by the Sponsor. A record of all vials of study drug received and administered will be maintained on an investigational drug inventory form provided by the Sponsor. The following information will be recorded:

- Date and quantity of study drug received
- Date and quantity of study drug dispensed from the pharmacy per patient
- Date and quantity of study drug administered to each patient (the start and stop date/time of infusion of drug should be recorded for each patient at each dose)
- Date and quantity of study drug destroyed (if prepared and dispensed, but not administered for any reason, the study drug may not be returned to inventory)
- Date and quantity of study drug returned to sponsor

Each shipment of study drug will contain an invoice describing the amount of drug shipped to the investigational site. The information on the invoice will be verified against the actual amount of drug received, after which the Investigator or the Investigator's designee will place the invoice in the Investigator's file.

During monitoring, the Sponsor's monitor will reconcile the information on the investigational drug inventory form with the actual amount of study drug remaining at each site. At the conclusion of the study, the monitor will perform accountability on all unused vials of study drug. Once accountability is complete, destruction may be performed at the site, or if the site does not have a destruction process, the monitor may ship the supplies back to the sponsor. In case of destruction at the site, the method should be documented in the site files. Following use, empty vials of study drug may be destroyed according to local regulatory and environmental requirements. A record of any such destruction will be placed in the Investigator's file.

6.7 Concomitant 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. Patients should receive analgesics, antiemetics, antibiotics, anti-pyretics, and blood products as necessary. Although warfarin-type anticoagulant therapies are permitted, careful monitoring of coagulation parameters is imperative, in order to avoid complications of any possible drug interactions (see also Section 6.8). 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.

6.7.1 Granulocyte Colony Stimulating Factors

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan and nal-IRI. In patients with metastatic pancreatic cancer in the NAPOLI-1 study receiving irinotecan liposome injection/5-FU/LV, the incidence of grade 3 or 4 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to White patients [13 of 73 (18%)]. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia at the investigator's discretion. Prophylactic use of G-CSF will be permitted if patients are considered high risk in the opinion of the investigator [33] [34] [35].

6.7.2 Therapy for Diarrhea

Acute diarrhea and abdominal cramps, developing during or within 24 hours after nal-IRI 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 patients experiencing cholinergic symptoms during the study.

Diarrhea can be debilitating and on rare occasions is potentially life-threatening. Diarrhea should be managed according to institutional guidelines, or according to the guidelines developed by an ASCO panel for treating chemotherapy-induced diarrhea, abstracted in Table 14 below [36]. For a detailed algorithm of diarrhea management for chemotherapy-induced diarrhea, see Appendix 2.

Table 9: Recommendations for Management of Chemotherapy Induced Diarrhea

Clinical Presentation	Intervention
Diarrhea, any grade	Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea; 2 mg every 4 hours for 5-FU induced diarrhea): continue until diarrhea-free for ≥ 12 hours Oral electrolyte replacement
Diarrhea persists on loperamide for > 24 hours	Oral fluoroquinolone x 7 days
Diarrhea persists on loperamide for > 48 hours	Stop loperamide; hospitalize patient; administer IV fluids
ANC < 500 cells/μL, regardless of fever or diarrhea	Oral fluoroquinolone (continue until resolution of neutropenia)
Fever with persistent diarrhea, even in the absence of neutropenia	Oral fluoroquinolone (continue until resolution of fever and diarrhea)

6.8 Prohibited Therapy

The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan:

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

Treatment with these agents and any others that interact with irinotecan, 5-FU, or oxaliplatin should be avoided wherever possible. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. No live attenuated vaccines should be given to patients of the study (e.g., yellow fever vaccine and polio virus vaccine). Refer to the country specific package inserts of 5-FU, leucovorin, or oxaliplatin for any other drug interactions.

The following therapies are not permitted during the study treatment phase:

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

(b) Potentially curative radiotherapy; palliative radiotherapy is permitted

(c) Any other investigational therapy

7 STUDY PROCEDURES

7.1 Protocol Visits

7.1.1 Screening Visit

The screening phase will begin once the patient signs the informed consent form. All procedures for screening and baseline are outlined in Section 8. For further descriptions of the clinical and laboratory assessments required, please refer to Sections 7.2 and 7.3 respectively.

7.1.2 On-Study Visits

Patients who are confirmed to meet all inclusion and exclusion criteria will be enrolled in the study and receive the first dose (Cycle 1 Day 1). All study procedures and assessments are

outlined in Sections 7.2, 7.3 and 8. During the treatment period, a window of ±2 days will apply to all visits, unless otherwise stated.

7.1.3 End of Treatment Visit

All patients must complete an End of Treatment (EoT) assessment at the time the Investigator removes the patient from treatment. This assessment should occur approximately 30 days (± 14 days) after the last dose of study treatment. All procedures and assessments are outlined in Section 8.

7.1.4 Long-term Follow-up

After the End of Treatment visit, patients should continue to be followed for survival status once every 8 weeks (± 7 days) via telephone, email, clinic visit, or medical record review until death, lost to follow-up, 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 patients who are discontinued for reasons other than progressive disease per RECIST v1.1, disease evaluations (including imaging studies) should continue into the follow-up period, as described in Section 7.2.6 below.

If a patient does not respond to the overall survival follow-up contacts, at least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient does not respond to these requests, the date of death may be captured from public records.

7.2 Clinical Procedures

7.2.1 Medical History

A medical history will include all pertinent prior medical conditions, surgeries or other medical procedures.

7.2.2 Vital Signs

Vital signs will include height (at screening only), weight, resting blood pressure, pulse, respiratory rate and temperature.

7.2.3 Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be obtained at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening, by the Investigator or his/her designee via questioning of the patient about their functional capabilities. Additionally, Karnofsky Performance Status (KPS) will be recorded at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening. See Appendix 3 for KPS and Appendix 4 for ECOG scales.

7.2.4 Electrocardiogram (ECG)

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 (see Section 6.5.2 for QTc in relation to diarrhea).

7.2.5 Adverse Event and Hospitalization Assessment

Investigators should complete all routine and standard of care assessments to evaluate for toxicity and symptoms of drug-induced adverse events. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings. The period for treatment-emergent adverse events and safety findings will be from the time of first study drug administration to 30 days after the date of last study drug administration. For detailed information on adverse event reporting, see Section 9. In addition, information on

patient hospitalizations and/or hospital visits should also be collected, whether or not associated with an adverse event.

Patients who continue infusion of 5-FU in home settings for the extended durations during the study, should keep a record of date/time of infusion start and stop and report any adverse events to the site. The Investigator or medically qualified person should call the patients who are discharged home for extended infusions to record the start and stop date/time for infusion and to assess adverse events reported by the patient (see Section 6.2.4.1).

7.2.6 Disease Evaluation

Tumor response will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 [37], to establish disease progression by CT or MRI. 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 v1.1 guidelines. Follow up measurements and overall response should also be in accordance with these guidelines.

Tumor assessments should be completed until it has been determined that the patient has progressive disease (in accordance with RECIST v1.1). For patients who do not have documented disease progression per RECIST v. 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. Continued imaging follow-up on schedule is recommended to reduce potential bias in the evaluations of the impacts of the experimental treatments on disease [38].

7.3 Laboratory Procedures

Laboratory assessments required for screening and enrolment eligibility can be performed locally for evaluating patient eligibility and enrolment only.

7.3.1 Complete Blood Count

A complete blood count (locally assessed) will include a white blood count (WBC) and differential, hemoglobin, hematocrit and platelet count.

7.3.2 Serum Chemistry

Serum chemistry will be assessed centrally, and will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, direct and total bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), uric acid, total protein, albumin, calcium, magnesium and phosphate. Chemistry may also be assessed locally, and local lab results may be used for enrollment and treatment decisions, if central lab results are not available.

7.3.3 CA19-9

CA19-9 biomarker levels will be measured centrally for all patients.

*7.3.4 UGT1A1*28*

A whole blood sample will be collected and assessed centrally at baseline to test for UGT1A1*28 allele status. The result is not needed prior to the initial dose of nal-IRI.

7.3.5 Biomarker Samples

Archived tissue samples, whole blood, serum and plasma will be collected to potentially identify factors that may correlate with tumor response, sensitivity or resistance to nal-IRI, and nal-IRI PK. Examples of potential analyses include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), enzyme levels (e.g. MMP9).

7.3.6 Urine or Serum Pregnancy Test

A urine or serum pregnancy test will be obtained for all females of childbearing potential at screening, at the start of each cycle during study treatment, and at the EoT visit. Exempt female patients will include those who have undergone a bilateral oophorectomy or hysterectomy or who are menopausal (defined as absence of a menstrual cycle for at least 12 consecutive months).

7.3.7 Pharmacokinetic Assessments

Since the combination of nal-IRI and oxaliplatin has not yet been tested in the clinic, plasma samples will be collected to determine the levels of nal-IRI and SN-38, as well as 5-FU and oxaliplatin, in patients. Additional analytes which may impact the pharmacokinetics of nal-IRI may also be measured from this sample. Directions for processing and shipping the PK plasma samples can be found in the study manual. The PK time points outlined in Table 10 below will be drawn during Cycle 1 only. PK samples will be collected during the study.

Table 10: Summary of PK Timepoints

Sample	Time-point	Window	Number of Draws[a]
1	Prior to nal-IRI infusion on Day 1 (pre-dose)	-24 hours	3
2	At the end of the nal-IRI infusion	+30 mins	1
3	At the end of the oxaliplatin infusion	+ 5 mins	2
4	Within 2 hours prior to the completion of the 5-FU infusion	-	3
5	+168 hours/7 days after the completion of the nal-IRI infusion	±24 hours	2
6	Prior to nal-IRI infusion on Day 15 (pre-dose)	-24 hours	2
7	End of Treatment visit (30 days post-last dose)	± 14 days	2

[a] The number of draws corresponds to the number of analytes that will be measured; for example, sample #3 at the end of the oxaliplatin infusion will be used to measure nal-IRI and oxaliplatin.

8 SCHEDULE OF ASSESSMENTS

Procedure	Screening Phase	Treatment Phase								Follow Up Phase	
	-28d	Cycle 1[19]				Additional Cycles[19]			Every 8w after 1st dose	End of Treatment Visit[18]	Every 2 months from EoT Follow-up visit
		D1	D3	D8	D15	D1	D8	D15			
Informed consent	X										
Medical history	X[1]										
Demographics	X[1]										
Vital signs	X[2]	X		X	X	X		X		X	
ECOG PS	XX[2, 23]	X				X				X	
KPS PS	XX[2, 24]										
CBC[4]	X[2]	X		X	X	X	X	X		X	
Serum chemistry[4]	X[2, 25]	X		X	X	X		X		X	
CA19-9	X[2]								X[17]	X[20]	
UGT1A1*28	X[2, 5]										
Pregnancy test	X[2]	X				X				X	
ECG[6]	X[1,7]									X	
Archived slides[8]	X										
Plasma for PK		X[9]	X[10]	X[11]	X[12]					X[26]	
Biomarker analysis[12, 13]		X[13]				X				X	
Concomitant meds and procedures	X[1]	X	X	X	X	X	X	X		X	
Dosing[14]		X			X	X		X			
AE / Hospitalization assessment & reporting	X[15]	X	X	X	X	X	X	X		X	
Disease evaluation[16]	X[1]								X[17]	X[18]	X[21]
Overall Survival											X[22]

[1] Procedures to be completed within 28 days of 1st dose of study drug
[2] Procedures to be completed within 7 days of 1st dose of study drug
[3] HRQL questionnaires must be completed before study treatment administration
[4] After screening, samples should be obtained within 2 days from scheduled date of collection
[5] Result not required prior to enrollment in the study or prior to receiving the initial dose of nal-IRI
[6] To be repeated as clinically indicated during the study
[7] Two independent readings at least 1 minute apart

[8] Collection of archived tumor block or paraffin embedded slides is required, if available
[9] Samples collected at the following timepoints: pre-dose (within 24 hours prior to nal-IRI infusion); at the end of the nal-IRI infusion (+30 mins) and at the end of the oxaliplatin infusion (+5 mins).
[10] Sample collected within 2 hours *prior* to the completion of the 5-FU infusion.
[11] Sample collected +168 hours/7 days after the completion of the nal-IRI infusion (±24 hours).
[12] Sample collected just prior to dosing with nal-IRI (within 24 hours).
[13] Blood will be collected for biomarker analyses: plasma samples will be collected at all timepoints; additionally, whole blood and serum samples will be collected on Cycle 1 Day 1 only.
[14] Study drug administration should occur ±2 days from scheduled date of administration
[15] Adverse events that occur during screening should be documented as pre-existing conditions; only SAEs that are felt by the Investigator to be directly related to a study procedure should be reported during screening.
[16] Disease evaluation according to RECIST v. 1.1 (see Section 7.2.6)
[17] Disease evaluations and CA19-9 should be done every 8 weeks (± 7 days) after 1st dose
[18] Unless completed in the prior 8 weeks
[19] All cycles are 28-day cycles, unless modified due to toxicity
[20] The End of Treatment (EoT) Follow-Up visit should occur 30 days (± 14 days) after last dose
[21] For patients who discontinue the study for reasons other than radiologically confirmed disease progression only (e.g. patients who are removed due to adverse events), imaging studies should be continued until documented progression of disease per RECIST v1.1 (see Section 7.2.6).
[22] Follow-up contacts should be made every 8 weeks (± 7 days) until death or study completion; data collected should include overall survival status as well as subsequent treatment information.
[23] ECOG to be performed at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening. ECOG assessment requires determination by two independent assessors. In the case of a discrepancy between the 2 assessments, the one with a lower score will be selected at each assessment.
[24] KPS to be performed at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening. KPS assessment requires determination by two independent assessors. In the case of a discrepancy between the 2 assessments, the one with a lower score will be selected at each assessment.
[25] Serum albumin needs to be collected at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening to confirm exclusion criteria 'p' (both labs at screening and prior to first dose may be confirmed locally) (Section 5.2).
[26] Sample to be collected within 5 minutes after ECG recording

9 ADVERSE EVENT REPORTING

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, including abnormal laboratory findings, symptoms, or diseases temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Worsening of a medical condition for which the efficacy of the study drug is being evaluated will not be considered an adverse event.

9.1.2 Unexpected Adverse Event

An unexpected adverse event is one for which the nature or severity of the event is not consistent with the applicable product information, e.g., the Investigator's Brochure, or the package insert or SmPC for approved therapies (see also Section 6.2.4).

9.1.3 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The term "severe" is often used to describe the intensity (severity) of an event; the event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

9.2 Documenting Adverse Events

SAE reporting will begin on the date the patient provides informed consent to participate in the study, however only those SAEs occurring prior to study drug administration, that the Investigator believes to be related to a protocol procedure, should be reported according to Section 9.3 below. All AEs that occur during the screening phase should be documented as pre-existing conditions. Treatment-emergent adverse event reporting will begin as of the administration of study drugs. The Investigator should elicit information regarding the occurrence of adverse events through open-ended questioning of the patient, physical examination, and review of laboratory results.

All adverse events, whether serious or not, will be recorded in the source documents and the adverse event page of the case report form (except as noted below). All new events, as well as those that worsen in intensity or frequency relative to baseline, must be recorded throughout

the study, until the End of Treatment follow-up visit. Adverse events should be followed through resolution, where possible. However, new adverse events felt by the Investigator to be related to the study treatment, must be reported any time the Investigator becomes aware of such an event, even if this occurrence is more than 30 days after the last dose of study drug.

Laboratory or vital signs abnormalities are to be recorded as Adverse Events only if they are clinically significant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

Information to be reported in the description of each adverse event includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event
- The date of resolution of the event
- A determination of whether the event is serious or not
- Action taken: none; change in the study drug administration (e.g., temporary interruption in dosing); drug treatment required; non-drug treatment required; hospitalization or prolongation of hospitalization required (complete serious adverse event page); diagnostic procedure performed; patient discontinued from the study (complete Final Visit section of the case report form)
- Outcome: resolved without sequelae; resolved with sequelae; event resolving; event ongoing; patient died (notify the Sponsor immediately, and complete the Serious Adverse Event page and the Final Visit section of the case report form)

9.3 Reporting Serious Adverse Events

All fatal or life-threatening adverse events must be reported to the medical monitor immediately by telephone, e-mail, or fax. Within 24 hours of knowledge of the event, the Serious Adverse Event Form must be faxed to the appropriate contact whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known. Source documentation of all examinations, diagnostic procedures, etc., which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

In case of accidental or intentional overdose of any of the study drugs, even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor immediately (within 1 working day) using the AE and SAE forms. Overdose will be defined as ≥133% of planned dose.

All other serious adverse events must be reported to the appropriate contact within 24 hours of becoming aware of the event by phone, e-mail or fax. The Serious Adverse Event Form must also be faxed to the appropriate contact within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known.

The medical monitor shall be contacted as deemed necessary by the site. Current contact information shall be maintained at the site within the regulatory binder.

All SAEs will be evaluated by the medical monitor. If meeting the requirements for expedited reporting, the Sponsor will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other Investigators involved in clinical trials with the study drug. The Investigator is responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) or Ethics Committee (EC), as per local regulations.

9.4 Determining the Severity and Relatedness of Adverse Events

9.4.1 Grading the Severity of an Adverse Event

Each adverse event will be graded according to the NCI CTCAE Version 4.03, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening or fatal which correspond to Grades 1, 2, 3, 4 and 5, respectively on the NCI CTCAE, with the following definitions:

- **Mild**: an event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate**: an event not resulting in disability or incapacity but which requires intervention;
- **Severe**: an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening**: an event in which the patient was at risk of death at the time of the event
- **Fatal**: an event that results in the death of the patient

9.4.2 Relatedness to Study Drug

- The Investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of the study drug. This relationship should be described as related or non-related.

9.4.3 Reporting and Follow-Up of Pregnancy

Patients who become pregnant while on study must immediately discontinue study treatment, and the pregnancy must be immediately reported to the medical monitor. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the Sponsor.

The Investigator should inform the patient of the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event of a pregnancy occurring in the partner of a male patient participating in the study, the pregnant partner should be requested to report the pregnancy to the Sponsor. The partner should also be informed of the risks of continuing with the pregnancy, the possible effects on the fetus, and be followed until conclusion of the pregnancy.

10 DATA MANAGEMENT AND STATISTICAL ANALYSIS

10.1 Case Report Forms

All data for the patients recruited for the trial will be entered onto electronic case report forms (eCRFs) via an Electronic Data Capture (EDC) system provided by the Sponsor. Only authorized staff may enter data onto the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the site staff.

10.2 Data Quality Assurance

Electronic CRFs will be checked for correctness against source document data by the Sponsor's monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the Investigator or the study site staff to make appropriate corrections, and the corrected eCRF will again be reviewed for completeness and consistency. Any discrepancies will be noted in the CRF system by means of electronic data queries. Authorized site staff will be asked to respond to all electronic queries according to the eCRF guidelines. Additional computer programs that identify selected protocol violations, out-of-range data and other data errors may be used to help monitor the study.

10.3 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the Sponsor. The SAP may modify the analysis outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

Categorical variables will be summarized by frequency distributions (number and percentage of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Testing will be conducted using a one-sided 0.10 significance level unless stated otherwise.

10.4 Study Populations

Patient populations defined for this study are described below:

- Safety (SAF) population: The safety population includes patients receiving at least one dose of any study drug
- PK Population: The PK population will include all nal-IRI treated patients who received at least 1 dose and who have at least 1 plasma concentration and no major protocol deviations affecting PK variables.

10.5 Disposition and Baseline Characteristics

Study populations (safety, PK) will be summarized and displayed as frequencies. Disposition of patients will be summarized including patients screened, treated, and discontinued. Reasons for discontinuation will be tabulated. Demographic and baseline characteristics will be summarized. Medical history and prior medications will be tabulated.

10.6 Efficacy Analysis

Efficacy analyses will be performed on Safety population.

Tumor evaluation will be measured according to RECIST v1.1. For each patient, progression free survival time will be determined as the time from the date of first study drug to the first documented radiographical progression of disease (PD), per investigator using RECIST 1.1, or death from any cause, whichever comes first. If the progression or death occurs at a time point that is greater than 16 weeks after the non-PD last tumor assessment, then progression-free survival time will be censored at the time of the last non-PD tumor assessment. Details on censoring rules will be provided in the study statistical analysis plan.

Efficacy Analysis

PFS will be analyzed using Kaplan-Meier method and descriptively summarized at 3 months interval for each dose level cohort. Median PFS time and corresponding 95% confidence limits will be presented.

Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from the first dose of study drug. Overall Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. The estimates of overall response rate and its corresponding 95% CI will be calculated for each dose level cohort.

A patient will be classified as having achieved disease control at 16 weeks if the patient has not progressed at the Week 16 assessment, i.e. has no PD up to and including the Week 16

assessment with documented non-PD (SD, PR, or CR) assessment. Patients who die, discontinue tumor assessments, or start new anti-cancer treatment prior to Week 16 will be considered as not having achieved DCR at Week 16. The disease control rate at 16 weeks (DCR_{16}) for a treatment group/cohort will be estimated by the number of patients who achieve disease control at 16 weeks divided by the number of patients treated.

Overall Survival (OS) is the time from the date of first study drug to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. Similar to PFS, OS will be analyzed using Kaplan-Meier method and descriptively summarized for each dose level cohort.

10.7 Safety Analysis

Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported by the MedDRA Version 17.1 or higher. Toxicity will be graded according to the NCI CTCAE Version 4.03.

Safety analysis of patients will include a summary of dose-limiting toxicity events.

The period for treatment-emergent adverse events and safety findings will be from the time of first study drug administration to 30 days after the date of last study drug administration. If an adverse event begins on the date of first study drug administration with no time recorded, the event will be considered as treatment-emergent.

Tabular summaries will be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study drug discontinuation, TEAE-related to study drug and TEAE Grade 3/4. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient.

Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so. Maximum and minimum decrease/increase in continuous laboratory data will be reported. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) will be assessed. Shift to most severe toxicity grade will be summarized.

Vital signs and ECG will be tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

10.8 Biomarker Analysis

Analyses will be performed to assess the associations between potential biomarkers (from plasma, serum, and archived tissue) and efficacy parameters (ORR, percent change in target lesion size, and PFS or as appropriate). Graphical displays will be performed when appropriate.

10.9 Pharmacokinetics Analysis

Plasma concentrations of total irinotecan, SN-38, and oxaliplatin and 5-FU in the combination therapies will be used to characterize corresponding PK parameters using a nonlinear mixed effects approach. Individual PK parameters will be estimated if warranted by the data. Graphical exploration will be performed to investigate any relationship between PK and pharmacodynamic endpoints. If a trend is shown, PK/PD modelling will be performed and reported separately.

10.10 Sample Size Justification

The total number of patients enrolled in the study will depend on the number of patients examined within each dose level cohort, as determined by the DLT Committee. Progression to the next dose level cohort will depend on the background toxicity rate (i.e., probability of DLT at a given dose). When 1 of 3 patients develops a DLT and the cohort is expanded to a minimum

of 6 patients, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of <10%. The table below shows the probability of escalation from cohort to cohort with various toxicity rates.

Table 11: Probability to Escalate as a Function of Toxicity Rate

Background Toxicity Rate	1%	5%	10%	20%	30%	40%	50%
Probability of Dose Escalation	0.999	0.973	0.906	0.709	0.494	0.309	0.172

A selected dose level cohort will be expanded to include 30 patients in total. An estimate of the DCR at Week 16 will be tabulated and summarized. Table 12 displays the probabilities of outcomes for DCR_{16} with n=30 as a function of the true DCR_{16}:

Table 12: Probability probabilities of outcomes for DCR_{16}

True DCR_{16}	Probability observed DCR_{16} ≥ 50%	Probability observed DCR_{16} ≥ 55%	Probability observed DCR_{16} ≥ 60%
45%	0.36	0.14	0.07
50%	0.57	0.29	0.18
55%	0.77	0.50	0.36
60%	0.90	0.71	0.58
65%	0.97	0.87	0.78
70%	0.99	0.96	0.92

11 EXTENSION PHASE

Following fulfillment of analysis requirements for the primary and/or secondary endpoints, the Sponsor may elect to transition patients that are still receiving treatment or are being followed for OS to an extension phase of the study.

Patients will continue to be followed for OS every 4 months.

Patients still receiving treatment will continue to receive this until disease progression, death, unacceptable study medication related toxicity or withdrawal of consent (see Section 5.3 for other discontinuation criteria).

For patients receiving treatment in the extension phase of the study only OS and treatment-related SAEs will be collected in the eCRF. In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and procedures) may be requested by the Sponsor in order to evaluate the reported SAE, though this additional information does not need to be captured in the eCRF. Investigators may perform standard procedures and tests needed to treat and evaluate patients; however, the results of these assessments will not be routinely reported. The extension phase of the study will be completed once all patients have died, withdraw consent, or lost to follow-up after two attempts on OS follow-up.

12 STUDY ADMINISTRATION

12.1 Pre-Study Documentation

Prior to initiating the trial, the Investigator will provide to the Sponsor or designee the following documents:

- A signed FDA Form 1572
- A current (i.e. updated no more than 24 months prior) curriculum vitae for the Principal Investigator

- A copy of the current medical license for the Investigator
- A letter from the IRB/EC stipulating approval of the protocol, the informed consent document and any other material provided to potential trial participants with information about the trial (e.g., advertisements)
- A copy of the IRB/EC-approved informed consent document
- A signed Investigator Protocol Agreement
- A completed financial disclosure form for the Investigator

Additional documents that may be requested include:

- A current (i.e. updated no more than 24 months prior) curriculum vitae for each sub-Investigator listed on the FDA Form 1572
- A copy of the current medical license for each sub-Investigator
- A completed financial disclosure form for all sub-Investigators
- A current laboratory certification for the reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory
- The current IRB/EC membership list for the reviewing IRB/EC, or, where appropriate, the multiple project assurance number from the Federal Wide Assurance program (www.ohrp.osophs.dhhs.gov)

12.2 Source Documents

The Investigator will maintain records separate from the eCRFs in the forms of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The Investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms when the Sponsor's monitor visits the investigational site. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to enrollment in the study can be used to fulfill certain screening and baseline assessments. All information obtained from source documents will be kept in strict confidentiality. Source data sent as supporting documentation for serious adverse events will be de-identified to preserve confidentiality.

12.3 Trial Ethics

The study will be performed according to the principles of the Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm), the International Conference on Harmonization Guidance on Good Clinical Practice and the requirements of the US FDA and/or local regulatory authorities regarding the conduct of human clinical trials.

12.4 Patient Informed Consent

No study related procedures will be performed until a patient or a patient's legal representative has given written informed consent. The Sponsor will provide to the Investigator a sample informed consent document that includes all the requirements for informed consent according the ICH GCP, U.S. FDA guidelines (21 CFR 50) and/or local regulatory or other country specific guidelines. However, it is up to the Investigator to provide a final informed consent that may include additional elements required by the Investigator's institution, and that has been IRB or EC approved. The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. Each

patient who agrees to participate in the trial and who signs the informed consent will be given a copy of the signed, dated and witnessed document (the witness signature is only required for cases that fit the criteria for needing a witnessed signature). The provision of informed consent will be documented in the medical record.

12.5 Investigational Review Board/Ethics Committee Approval

The trial will not be initiated until there is approval of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial by the local/central IRB or EC. The IRB/EC should be duly constituted according to local regulatory or other country specific requirements. Approval must be in the form of a letter signed by the Chairperson or the Chairperson's designee, must be on official stationary and must include the protocol by name and/or by designated number. If an Investigator is a member of the IRB/EC, then the approval letter must stipulate that the Investigator did not participate in the final vote, although the Investigator may participate in the discussion of the trial. The Investigator will also inform the IRB/EC of any SAEs that the Sponsor reports to regulatory authorities, will report on the progress of the trial at least yearly (or more frequently if required by local regulation or guidance) and will provide to the IRB/EC a final summary of the results of the trial at the conclusion of the trial.

12.6 Monitoring

A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the trial. The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. The Investigator will allow the Sponsor or designee access to all pertinent medical records, as required by federal or other country specific regulations, in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process. Monitoring visits will be conducted according to a study monitoring plan, and will include review of various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor.

In addition to the above, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The Investigator must promptly inform the Sponsor of any audit requests by health authorities, and will provide the Sponsor with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and locally applicable privacy regulations, a patient's authorization to use personally identifiable health information may be required for each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

12.7 Confidentiality

It is the responsibility of the Investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms and other documents submitted to the Sponsor must never contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRF's and any other material submitted to the Sponsor. All case report forms and any identifying

information must be kept in a secure location with access limited to the study staff directly participating in the trial.

12.7.1 Samples for Central Lab Testing

Samples collected for standard laboratory tests, including biochemistry, UGT1A1 and CA 19-9 testing will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

12.7.2 Confidentiality of Biomarker Samples

Blood samples collected as part of the biomarker analysis will be identified only by a number assigned to the patient at the study site; this number will be used in lieu of the patient's name in order to protect the patient's identity. The samples will be stored at a facility designated by the Sponsor. Other than the patient's unique identifying number, no additional patient information that could potentially disclose the patient's identity will be stored with these samples. Samples will be kept until they are used completely for the specified biomarker analyses, or, in the event there is remaining tissue or blood sample available, such specimens will be stored for a maximum of 5 years after approval of the final study report for the clinical trial; at that time, any remaining samples will be destroyed. Patients may withdraw consent from the study at any time. However, data already collected will not be removed from the study dataset.

The results from these exploratory analyses may not necessarily be shared with the Investigators or the participating patients.

12.8 Protocol Amendments

The protocol will only be amended with the consent of the Sponsor and the IRB/EC. Changes to the protocol must be in the form of a written amendment; changes other than those of a simple administrative nature (e.g., a new telephone number for a medical monitor) must be submitted by the Investigator to their IRB/EC and such amendments will only be implemented after approval of the requisite IRB/EC. All amendments will also be submitted to the FDA and local regulatory authorities by the Sponsor.

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the Investigator immediately. The Investigator must then immediately inform the Sponsor and local IRB or EC; the Sponsor will immediately notify local regulatory authorities.

12.9 Publication

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

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.

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.

12.10 Records Retention

The Investigator will retain the records of the clinical trial (including, but not necessarily limited to, CRFs, source documents, informed consent forms, drug accountability records, IRB/EC correspondence, Sponsor correspondence, etc.) for 2 years following the date that the last marketing application for the study drug is approved, or if no marketing application is filed, or if such an application is not approved, for 2 years after the formal discontinuation of clinical development of the study drug. The Sponsor or designee will notify Investigators when retention of study records is no longer required. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary.

Study records must be retained as per the GCP guidelines and local regulatory requirements, including, but not limited to, case report forms, signed informed consents, correspondence with the IRB/EC, study drug dispensing and inventory records, source documents (clinic charts, medical records, laboratory results, radiographic reports) and screening/enrollment logs.

Should the Investigator relocate or retire the responsibility for maintaining the study records may be transferred to another Investigator. The Sponsor must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the site is willing to assume this responsibility, the Sponsor will assume responsibility for maintaining the study records.

12.11 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 enrollment
- Safety concerns
- Drug supply or manufacturing issues
- The Sponsor's decision to modify or discontinue the development nal-IRI
- A request to discontinue the study by the FDA and/or local regulatory authorities.

The Sponsor will promptly inform all Investigators and the FDA and/or local 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.

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14 INVESTIGATOR AND SPONSOR SIGNATURE PAGE

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the patients in the study.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice.

Signature of Investigator

Date

Print Name of Investigator

On behalf of the Sponsor

PPD

Oncology

Ipsen Bioinnovation

Date

APPENDICES

Appendix 1: 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 [39]:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - oral
  - injectable
  - implantableb
- intrauterine device (IUD)[b]
- intrauterine hormone-releasing system (IUS)[b]
- bilateral tubal occlusion[b]
- vasectomized partner[b,c]
- sexual abstinence[d]

[a] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method. For hormonal contraception methods, caution should be taken to possible interaction with a non-biologic investigational medicinal product (IMP). Interaction leading to reduced efficacy of the hormonal contraception method can occur due to increased metabolism (i.e. enzyme induction).

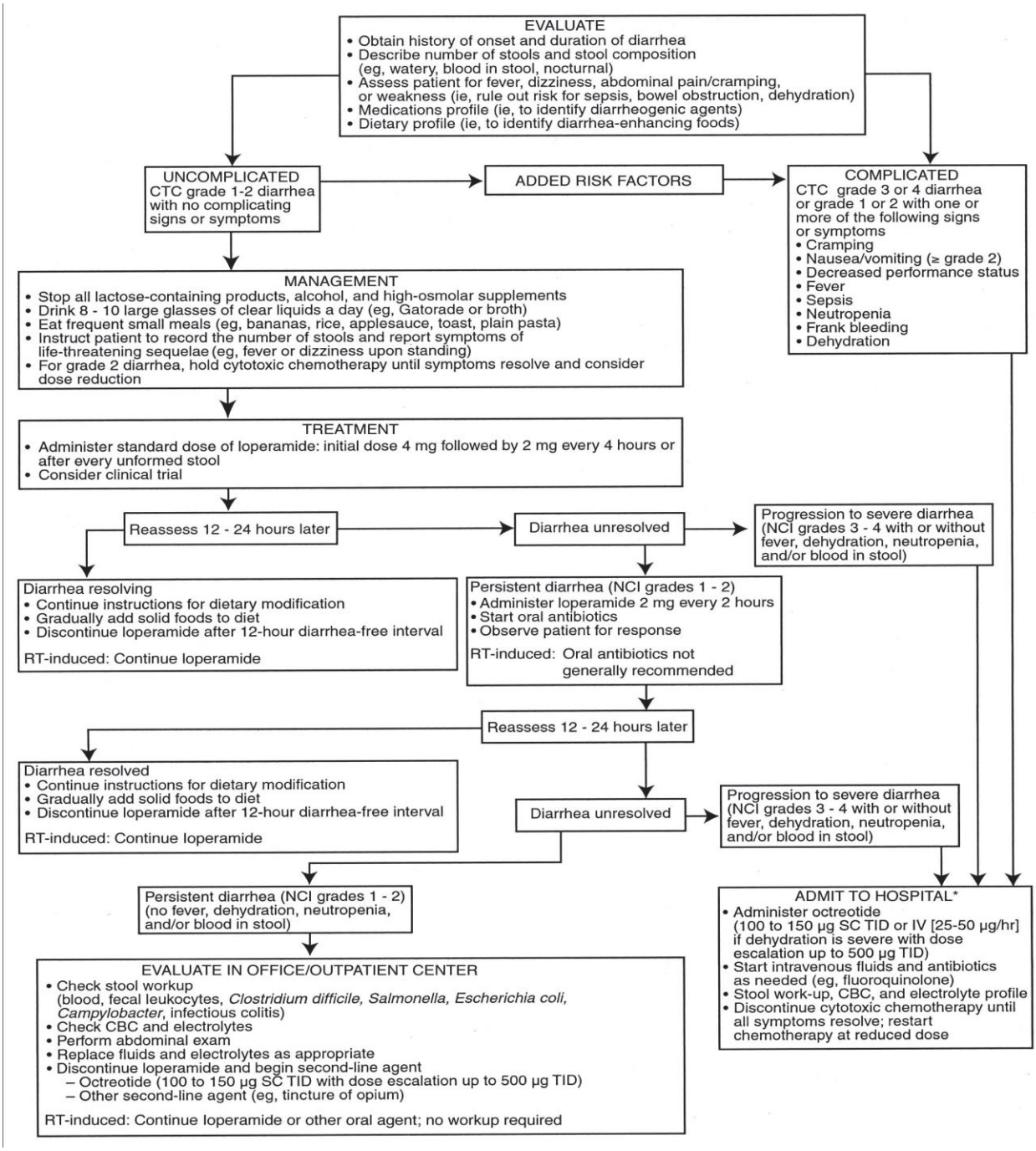
b Contraception methods that in the context of this guidance are considered to have low user dependency.

c Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

d 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 patient

Note: A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Appendix 2: Proposed Algorithm for Diarrhea Management



Proposed algorithm for the assessment and management of treatment-induced diarrhea.

Note: For radiation-induced cases and select patients with CID, consider intensive outpatient management, unless the patient has sepsis, fever, or neutropenia. CTC, Common Toxicity Criteria; NCI, National Cancer Institute; RT, radiotherapy; SC, subcutaneous; tid, three times per day; IV, intravenous; CBC, complete blood count; CID, chemotherapy-induced diarrhea [36].

Appendix 3: Karnofsky Performance Status

Karnofsky Status	Karnofsky Grade
Normal, no complaints	100
Able to carry on normal activities. Minor signs or symptoms of disease	90
Normal activity with effort	80
Care for self. Unable to carry on normal activity or to do active work	70
Requires occasional assistance, but able to care for most of his needs	60
Requires considerable assistance and frequent medical care	50
Disabled. Requires special care and assistance	40
Severly disabled. Hospitalisation indicated though death non imminent	30
Very sick. Hospitalisation necessary. Active supportive treatment necessary	20
Moribund	10
Dead	0

Appendix 4: 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 5: Summary of Changes 28 December 2016 (Version 3.1) to 29 September 2017 (Version 5.0)

STUDY NUMBER:	MM-398-07-02-03
PROTOCOL TITLE:	**A RANDOMIZED, OPEN-LABEL PHASE 2 STUDY OF NANOLIPOSOMAL IRINOTECAN (NAL-IRI)-CONTAINING REGIMENS *VERSUS* NAB-PACLITAXEL PLUS GEMCITABINE IN PATIENTS WITH PREVIOUSLY UNTREATED, METASTATIC PANCREATIC ADENOCARCINOMA**
AMENDED PROTOCOL VERSION NUMBER & DATE	Version 5.0, 29 September 2017

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED: Minor formatting, typos and rephrasing of text to enhance clarity have not been recorded.

Version Date		**28 DECEMBER 2016 (VERSION 3.1)**	**29 SEPTEMBER 2017 (VERSION 5.0)**
Page	**Section**	**WAS**	**IS**
Throughout	Header Title page Signature page	The study Sponsor is Merrimack Pharmaceuticals.	The study Sponsor is Ipsen Bioscience. *The protocol header, confidentiality statement and protocol signatory were updated to reflect this change.* *These changes were incorporated in Version 4.0 (dated 03 April 2017) of the protocol, which is now superseded by Version 5.0.*
Throughout	Synopsis 3.1, 3.2.1, 3.2.2, 4.2, 4.2.1, 4.2.2, 4.3, 10.6 & Figure 1	The study is divided into two parts: Part 1 and 2. Part 1 referred to as the 'safety run in period' consisting of the dose escalation phase enrolling small cohorts of patients. Part 2 refers to the randomised open label comparative three arm phase (Arm 1, Arm 2 and Arm 3).	The study is divided into two parts: Part 1 and 2 (*the use of Arm 1 was reserved for use in the context of Part 2 only*). *Part 1 of the study is split into two phases: Part 1A (dose escalation phase enrolling small cohorts of patients progressively) and Part 1B (dose expansion intended to enroll 24 additional patients).* Part 2 refers to the randomised open label comparative three arm phase (Arm 1, Arm 2 and Arm 3).
Throughout	Synopsis 3.1, 3.2,		*As DLT within any cohort is potentially determined by a complex interaction between the respective dose levels of each drug*

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	3.2.3, 4.2, 4.3 & Table 6	Part 1 includes dose levels -1, 1, 2, -2A and -2B to be evaluated based on the defined escalation and de-escalation process (in which the dose for one of the three drugs (nal-IRI) will be increased while the other two drugs will maintain a constant dose) and the safety and tolerability of each dose level cohort.	*administered as part of a combination therapy, the sequence of dose level cohorts examined (-1 to -3) contains both dose escalation and dose de-escalation strategies for each individual drug, in order to control the total combined dose level within any given cohort. This means that for each individual drug, the dose level may decrease, increase or remain the same between successive cohorts.* *A new dose level cohort -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) is introduced for evaluation in Part 1A following the completion of three dose level cohorts (1, -1 and -2B). Dose level -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable, while dose levels 1 and -2B were considered to be not tolerable. Dose levels 2 and -2A will not be evaluated. If the dose level -3 is found to be safe and tolerable, the cohort will be expanded to include an additional 24 subjects. If the dose level -3 is not found to be safe and tolerable, the dose level cohort -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) will be expanded to include additional 24 subjects.* *Final determination of the Part 2 dose for Arm 1 will be made after all patients in the Part 1A (dose escalation) and Part 1B (expansion cohort) have completed two scheduled assessments.*
8 & 35	Synopsis & 2.1.2	**2.1.2 Secondary Objective** **Part 1:** • To characterize the pharmacokinetics (PK) of nal-IRI in combination with 5-FU and oxaliplatin	*Another secondary objective was added for the Part 1 evaluation.* **2.1.2 Secondary Objective** **Part 1:** • To characterize the pharmacokinetics of nal-IRI in combination with 5-FU + oxaliplatin • To evaluate efficacy signals with nal-IRI in combination with 5-FU/LV + oxaliplatin using overall response rate (ORR) [CR + PR, per RECIST v1.1], disease control rate (DCR) [CR +

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			PR + SD, per RECIST v1.1], duration of response, PFS, and OS
11-12 & 39	Synopsis & 3.2.2	**3.2.2 DLT Definition for Arm 1 (Nal-IRI + 5-FU/LV + Oxaliplatin)** • Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity	*The DLT criteria (bullet 3) was modified to avoid multiple replacements and assess the safety/tolerability in a timely and accurate fashion.* **3.2.2 DLT Definition for Part 1 (Nal-IRI + 5-FU/LV + Oxaliplatin)** • Any study regimen related adverse event that leads to a delay of the next scheduled study treatment dose for more than 14 days All patients will continue to be monitored for safety beyond Cycle 1, in order to determine if multiple cycles of treatment are tolerable. If any patient within a given cohort experiences a DLT in Part 1A, they may continue in the study at a lower dose level of oxaliplatin and/or nal-IRI, (as determined by the DLT Committee in accordance with Section 6.5) upon resolution of the relevant toxicity. Other patients in the same cohort who do not experience a DLT will continue with unmodified dose levels of oxaliplatin and/or irinotecan (unless a dose modification is judged to be necessary by the DLT Committee on safety grounds.
13 & 40	Synopsis & 4	**4 Enrollment and Treatment** Approximately 6-18 patients will be enrolled in Part 1. An additional 150 patients (50 patients per arm) will be enrolled during Part 2. The total enrollment for the study will be approximately 156-168 patients. Patients will be treated until disease progression (as determined by RECIST v1.1 criteria evaluated every 8 weeks from first dose of study drug), toxicity, or physician or patient's choice (see Section 5.3).	**4 Enrollment and Treatment** Approximately 54 patients will be enrolled in Part 1. An additional 150 patients (50 patients per arm) will be enrolled during Part 2. Therefore, the total enrollment for the study will be approximately 204 patients. All patients will be treated until disease progression (as determined by RECIST v1.1 criteria evaluated every 8 weeks from first dose of study drug), unacceptable drug related toxicity, or physician or patient's choice (see Section 5.3).
13-14	Synopsis		*Inclusion criteria a), b), c) and d) were modified based on the learnings of three completed dose level cohorts and inclusion*

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& 42-43	& 5.1	**5.1 Inclusion Criteria** a) Pathologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting: b) Measurable or non-measurable disease as defined by RECIST v1.1 c) ECOG performance status of 0 or 1 d) Adequate biological parameters as evidenced by the following blood counts: • ANC > 1,500 cells/µl without the use of hematopoietic growth factors, • Platelet count > 100,000 cells/µl, and • Hemoglobin > 9 g/dL j) Agreeable to submit unstained archived tumor tissue for analysis, if available	*criteria j) was removed (no changes were made to other inclusion criteria).* **5.1 Inclusion Criteria** a) Histologically or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting: b) At least one tumor lesion measurable by CT or MRI scan (according to RECIST v1.1 criteria) c) ECOG performance status of 0 or 1 at both Screening and within 72 hours prior to randomization. Two observers will be required to assess ECOG. If different, the lowest assessment will be used for the eligibility evaluation at each assessment d) Adequate biological parameters as evidenced by all of the following blood counts: • ANC > 1,500 cells/µl without the use of hematopoietic growth factors within last 7 days prior to Screening • Platelet count > 100,000 cells/µl • Hemoglobin > 9 g/dL; transfusion is allowed, provided interval is ≥ 7 days prior to Screening
14-15 & 43-44	Synopsis & 5.2	**5.2 Exclusion Criteria** a) Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed) b) Prior treatment of pancreatic cancer with cytotoxic doses of chemotherapy (patients receiving prior treatment	*Existing exclusion criteria a), b) and k) were modified and new exclusion criteria o), p) and q) were added based on the completion of previous 3 dose level cohorts (no changes were made to other exclusion criteria).* **5.2 Exclusion Criteria** a) Prior treatment of pancreatic cancer in the metastatic setting (or locally advanced setting, Part 1 only) with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed) b) Prior treatment of pancreatic cancer with cytotoxic doses of systemic anti-tumor therapy (patients receiving prior treatment

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		with chemotherapy as a radiation sensitizer are eligible if ≥ 6 months has elapsed from completion of therapy) k) Presence of any contraindications for 5-FU, leucovorin, or oxaliplatin	with chemotherapy as a radiation sensitizer are eligible if ≥ 6 months has elapsed from completion of therapy) k) Presence of any contraindications for 5-FU, leucovorin, oxaliplatin, gemcitabine or nab-paclitaxel o) Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma p) Documented serum albumin <3 g/dL at Screening Visit and within 72 hours prior to enrollment/ randomization (both labs at screening and prior to enrollment/randomization may be confirmed locally) q) Patients 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
44-45	5.3	**5.3 Patient Discontinuation** A patient may withdraw from the study at any time and for any reason. It is intended that patients will be treated until Investigator-determined progressive disease per RECIST v1.1 or unacceptable toxicity. Some possible reasons for early discontinuation of study treatment include, but are not limited to the following: • Progressive neoplastic disease per RECIST v1.1 • The patient experiences an adverse event which: o in the opinion of the Investigator, precludes further participation in the trial o requires treatment to be withheld for more than 14 days, unless in the opinion of the investigator the patient is receiving benefit from the study treatment o requires more than 2 dose reductions • Clinical and/or symptomatic deterioration	*Section 5.3 (Patient Discontinuation) was divided into Sections 5.3.1, 5.3.2 and 5.3.3.* **5.3 Patient Discontinuation** **5.3.1 Discontinuation of Study Treatment** It is intended that patients will be treated until radiologically determined progressive disease per RECIST v1.1 or unacceptable study drug related toxicity. However, a patient 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 v1.1 • Clinical deterioration sufficient to prevent further radiological assessment • A study drug related adverse event, prior to disease progression, which: o in the opinion of the Investigator, precludes further treatment with all study drugs o requires treatment with one or more study drugs to be withheld for more than 14 days, unless in the opinion of

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		• Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial • Significant noncompliance with the protocol per PI assessment • Withdrawal of consent • The Investigator removes the patient from the trial in the best interests of the patient • Study termination by the Sponsor • Use of prohibited concomitant medications • Patient is lost to follow up If a patient withdraws from the trial, a complete final evaluation at the time of the patient's withdrawal should be made with an explanation of the reason for withdrawal. Following treatment discontinuation for other reasons above, all procedures and evaluations required at the 30 day follow up visit should be completed. All patients who discontinue the trial as a result of an adverse event must be followed until resolution or stabilization of the adverse event. Overall survival follow-up contacts should continue every 2 months from the 30-day follow-up visit until death or study closure, whichever comes first. If a patient does not return to the clinic for follow-up visits, attempts should be made to contact the patient via phone, email, or mail. At least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient is considered lost to follow-up, the date of death may be captured from public records.	the investigator the patient is receiving benefit overall from the study treatment o would result in a third dose reduction in any single study drug (in a patient having already experienced 2 previous dose reductions) o requires discontinuation of nal-IRI (Arm I only) • Development of an intercurrent medical condition or need for concomitant therapy that precludes further treatment with all study drugs • Withdrawal of consent for further treatment • Pregnancy A patient who discontinues study medication has **not** withdrawn from the study and must continue with all ongoing protocol requirements, as detailed in Section 5.3.3. **5.3.2 Withdrawal from the Study)** A patient may withdraw, or be withdrawn, from the study at any time. Reasons for withdrawal from the study include, but are not limited to the following: • Significant noncompliance with the protocol, per Investigator's assessment • The Investigator removes the patient from the trial in the best interests of the patient • Use of prohibited concomitant medications • Patient is lost to follow up • Withdrawal of consent for further participation in the study • Death • Study termination by the Sponsor

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			5.3.3 Procedures following Study Drug Discontinuation or Study Withdrawal Following study drug discontinuation all procedures and evaluations required at the 30-day (End of Treatment) follow up visit should be completed. All patients who discontinue study medication as a result of an adverse event must be followed until resolution or stabilization of the adverse event. Patients who discontinue study drug 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 v1.1 has been documented. Overall survival follow-up contacts should continue every 2 months from the 30-day follow-up visit until death or study closure, whichever comes first. If a patient does not return to the clinic for follow-up visits, attempts should be made to contact the patient via phone, email, or mail. At least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient is considered lost to follow-up, the date of death may be captured from public records. If a patient withdraws from the study at any point, a complete final evaluation at the time of the patient's withdrawal should be made with an explanation of the reason for withdrawal. At the time of withdrawal from the study, it should be clarified with the patient whether they still consent to be followed up for survival status only (including where appropriate through publicly available records) and any such consent to ongoing survival follow up must be documented in both the source hospital records and the eCRF.
48	6.2.3	**6.2.3 Packaging and Labelling of Combination Therapies**	**6.2.3 Packaging and Labelling of Combination Therapies** Sites participating in this protocol will source their own combination therapy supplies. However, for sites where this is not

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		Commercially available 5-FU and leucovorin (*l* + d racemic form, or the levo-leucovorin *l* form), oxaliplatin, nab-Paclitaxel, and gemcitabine will be provided to enrolled patients in accordance with the specific treatment regimen in the respective arms. All patients who are enrolled to Arms 1 and 2 will be provided with 5-FU, leucovorin, and oxaliplatin, if applicable. All patients who are enrolled to Arm 3 will be provided with nab-Paclitaxel and gemcitabine, if applicable.	possible due to country legal or regulatory restrictions, Ipsen will provide commercially available 5-FU and leucovorin, oxaliplatin, nab-paclitaxel and gemcitabine as required by their enrolled patients for their specific treatment regimen. Ipsen sourced combination therapy supplies will be labeled in accordance with local regulatory requirements, and site accountability for all Ipsen sourced clinical trial material is required.
Throughout	Synopsis, 3.1, 3.2.2 6.5.2 7.3.4 8	Patients will be tested for UGT1A1*28 status during screening, however the result of the test is not required prior to the initial dose of nal-IRI. For Part 1 patients receiving 80 mg/m^2 of nal-IRI: depending on the overall safety profile seen after the first dose, the dose may be reduced to 60 mg/m^2 after discussion between the PI, Sponsor and Medical Monitor. Any Part 1 patients who receive a reduced dose during Cycle 1 due to UGT1A1*28 homozygosity will not be evaluable for the cohort and will be replaced. For Part 2, UGT1A1*28 7/7 homozygous and non-homozygous genotype patients should receive the full starting dose of nal-IRI; All Arm 1 subjects should start at	*Patients will be tested for UGT1A1*28 status during screening as a safety biomarker to further analyze the association between UGT1A1*28 homozygosity, SN-38 concentration and toxicity. However, the protocol does not contain formal recommendations on nal-IRI dose modifications as a consequence of homozygosity. The results of testing are not required prior to the first dose of nal-IRI but will be made available for review in Part 1 and the starting dose for all patients in Part 1 will be as per the dosing table (regardless of UGT1A1*28).* As part of this study, pharmacogenomic data will be collected on all patients for determination of UGT1A1*28 status**.** Importantly however, no grade 4 neutropenia was observed in patients homozygous for the wild-type (WT) 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 [25]). Population PK studies of nal-IRI have not identified a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure (see Investigator Brochure). In a Phase I study (UCSF 8603, as referenced in Table 2 above) no differences in toxicity were seen in cohorts of heterozygous or WT patients, and DLTs of diarrhea

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		60 mg/m^2, while all Arm 2 patients will begin dosing at 80 mg/m^2. Follow the tables above for guidance on dose modification due to toxicity.	with or without accompanying dehydration or fatigue, were seen in both cohorts. Because of these discrepancies in the severity of previously documented toxicity arising from UGT1A1*28 homozygosity, and because the prevalence of UGT1A1*28 homozygosity is relatively low, testing results will not be required prior to the first dose of nal-IRI on this study and the starting dose for all patients in Part 1 will be as described in Table 5. The protocol does not contain formal recommendations on nal-IRI dose modifications as a consequence of homozygosity. All patients should receive the full starting dose of nal-IRI. All Arm 1 patients should start at the dose level identified from Part 1, while all Arm 2 patients will begin dosing at 80 mg/m^2. The UGT1A1*28 status of each patient will subsequently be made available to individual investigators.
59	6.5.5	**6.5.5 Rules for Dose Omissions and Modified Schedules** The following guidance should be followed when all study drugs in any arm are held/missed: • If Day 1 doses are held/missed: the doses intended for Day 1 of a cycle should be delayed, such that the start of that cycle will not begin until the doses are actually administered to the patient • If Day 8 doses are held/missed (applies to Arm 3 only): the cycle will continue per protocol and those doses will be considered missed. • If Day 15 doses are held/missed: ○ **Arms 1 and 2 only:** if toxicity recovers within 7 days, the day 15 doses may be delayed and subsequently given 1 week late. The next cycle would then continue 14 days following the administration of the delayed Day 15 dose.	**6.5.5 Rules for Dose Omissions and Modified Schedules** The following guidance should be followed when all study drugs in any arm are held/missed: For both Part 1 and Part 2, the maximum delay between the date of a scheduled but missed dose and the planned next dose should be up to 14 days. In Part 2, Arm 3, • If Day 1 doses are held/missed: the doses intended for Day 1 of a cycle should be delayed, such that the start of that cycle will not begin until the doses are actually administered to the patient • If Day 8 doses are held/missed: the cycle will continue per protocol and those doses will be considered missed. • If Day 15 doses are held/missed: the dose will be considered missed and dosing will continue with Day 1 of the next cycle when toxicity recovers.

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		However, if the toxicity recovers between 7-14 days after scheduled Day 15 dose (i.e. dose is delayed for 2 weeks), that dose will be considered missed and Day 1 of the next cycle should occur as originally scheduled. ○ **Arm 3 only:** the dose will be considered missed and dosing will continue with Day 1 of the next cycle when toxicity recovers (e.g. if toxicity recovers within 7 days, that week will be considered the rest week, and the next cycle can begin 1 week after the previously scheduled Day 15 dose; alternatively, if the toxicity recovers between 7-14 days from the scheduled Day 15 dose, the Day 1 dose of the next cycle should occur as originally scheduled).	
63, 67-69 90	7.2.3, 8 & Appendix 3	Only ECOG performance status to be recorded at Screening and within 72 hours of enrollment/randomization	*In additional to the ECOG performance status, KPS was also to be recorded at Screening and within 72 hours of enrollment/randomization.* *An additional Appendix 3 was added for evaluating the KPS.*
81-82	12.9	As the Study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication report has been submitted for publication in a peer reviewed journal within twelve (12) months of the completion of this Study at all sites, the Investigator shall have the right to publish or present independently the results of this patient to the review	*Publication policy was updated as per Ipsen Bioscience standards:* The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor. The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee. The sponsor requires

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		procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least forty-five (45) days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed ninety (90) days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights. The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the Collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s). The Sponsor or its designee has the right at any time to publish the results of the Study.	that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material. 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. 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.
84-85	13		*Five new references were added to the reference list.* [28] R.W. Marsh, M.S. Talamonti, M.H. Katz and J.M. Herman, "Pancreatic cancer and FOLFIRINOX: a new era and new questions," Cancer Med., vol. 4, no. 6, pp. 853–863, Jun 2015.

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			[29] B. Chibaudel, F. Maindrault-Goebel, J.B. Bachet, C. Louvet, A. Zhalil, O. Dupuis, P. Hammel, M-L. Garcia, M. Bennamoun, D. Brusquant, C. Tournigand, T. André, C. Arbaud, A.K. Larsen, Y-W. Wang, C.G. Yeh, F. Bonnetain and A de Gramont, "PEPCOL: a GERCOR randomized phase II study of nanoliposomal irinotecan PEP02 (MM-398) or irinotecan with leucovorin/5-fluorouracil as second-line therapy in metastatic colorectal cancer," Cancer Med. vol. 5, no. 4, pp. 676-683, Apr. 2016. [32] T.J. Smith, K. Bohlke, G.H. Lymann, K.R. Carson, J. Crawford, S.J. Cross, J.M. Goldberg, J.L. Khatcheressian, N.B. Leighl, C.L. Perkins, G. Somlo, J.L Wade, A.J. Wozniak, American Society of Clinical oncology, "Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update," J Clin Oncol. Vol. 33, no. 28, pp. 3199-3212, Oct. 2015. [33] M.S. Aapro, J Bohlius, D.A. Cameron, L.D. Lago, J.P. Donnelly, N. Kearney, G.H. Lyman, R. Pettengell, V.C.Tjan-Heijnen, J. Walewski, D.C. Weber, C. Zielinski and European Organisation for Research and Treatment of Cancer "2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours," Eur J Cancer, vol. 47, no. 1, pp. 8 32, Jan. 2011. [34] J. Crawford, C. Caserta J, F. Roila; ESMA Guidelines Working Group, "Haematopoietic growth factors: ESMO Clinical Practice Guidelines. Ann Oncol, vol. 21 (Suppl 5), pp. v248-v251, May. 2010.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	MM-398-07-02-03	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Version 5.0, 29 September 2017**	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
OBJECTIVE(S) OF PROTOCOL AMENDMENT	1. To optimize the NAPOX regime (irinotecan liposome injection + 5-FU/LV + oxaliplatin) in patients with metastatic pancreatic adenocarcinoma by assessing an additional dose for the combination regimen (Part 1A) 2. To expand the study sample size (Part 1B), once the dose is selected from Part 1A, to further evaluate the safety and efficacy signals and update the study design accordingly 3. To adjust the inclusion and exclusion criteria based on learnings from the three completed dose level cohorts 4. To reflect the change in study Sponsor.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐ *(tick one)*

Appendix 6: Summary of Changes: 03 April 2017 (version 4.0) to 29 September 2017 (version 5.0)

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Through out	Synopsis 3.1, 3.2, 3.2.3, 4.2, 4.3 &		*As DLT within any cohort is potentially determined by a complex interaction between the respective dose levels of each drug administered as part of a combination therapy, the sequence of dose level cohorts examined (-1 to -3) contains both dose escalation and dose de-escalation strategies for each individual drug, in order to control the total combined dose*

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	Table 6	Part 1 includes dose levels -1, 1, 2, -2A and -2B to be evaluated based on the defined escalation and de-escalation process (in which the dose for one of the three drugs (nal-IRI) will be increased while the other two drugs will maintain a constant dose) and the safety and tolerability of each dose level cohort.	*level within any given cohort. This means that for each individual drug, the dose level may decrease, increase or remain the same between successive cohorts.* *A new dose level cohort -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) is introduced for evaluation in Part 1A following the completion of three dose level cohorts (1, -1 and -2B). Dose level -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable, while dose levels 1 and -2B were considered to be not tolerable. Dose levels 2 and -2A will not be evaluated. If the dose level -3 is found to be safe and tolerable, the cohort will be expanded to include an additional 24 subjects. If the dose level -3 is not found to be safe and tolerable, the dose level cohort -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) will be expanded to include additional 24 subjects.* *Final determination of the Part 2 dose for Arm 1 will be made after all patients in the Part 1A (dose escalation) and Part 1B (expansion cohort) have completed two scheduled assessments.*
8 & 35	Synopsis & 2.1.2	**2.1.2 Secondary Objective** **Part 1:** • To characterize the pharmacokinetics (PK) of nal-IRI in combination with 5-FU and oxaliplatin	*Another secondary objective was added for the Part 1 evaluation.* **2.1.2 Secondary Objective** **Part 1:** • To characterize the pharmacokinetics of nal-IRI in combination with 5-FU + oxaliplatin • To evaluate efficacy signals with nal-IRI in combination with 5-FU/LV + oxaliplatin using overall response rate (ORR) [CR + PR, per RECIST v1.1], disease control rate (DCR) [CR + PR + SD, per RECIST v1.1], duration of response, PFS, and OS

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11-12 & 39	Synopsis & 3.2.2	**3.2.2 DLT Definition for Arm 1 (Nal-IRI + 5-FU/LV + Oxaliplatin)** • Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity	*The DLT criteria (bullet 3) was modified to avoid multiple replacements and assess the safety/tolerability in a timely and accurate fashion.* **3.2.2 DLT Definition for Part 1 (Nal-IRI + 5-FU/LV + Oxaliplatin)** • Any study regimen related adverse event that leads to a delay of the next scheduled study treatment dose for more than 14 days All patients will continue to be monitored for safety beyond Cycle 1, in order to determine if multiple cycles of treatment are tolerable. If any patient within a given cohort experiences a DLT in Part 1A, they may continue in the study at a lower dose level of oxaliplatin and/or nal-IRI, (as determined by the DLT Committee in accordance with Section 6.5) upon resolution of the relevant toxicity. Other patients in the same cohort who do not experience a DLT will continue with unmodified dose levels of oxaliplatin and/or irinotecan (unless a dose modification is judged to be necessary by the DLT Committee on safety grounds.
13 & 40	Synopsis & 4	**4 Enrollment and Treatment** Approximately 6-18 patients will be enrolled in Part 1. An additional 150 patients (50 patients per arm) will be enrolled during Part 2. The total enrollment for the study will be approximately 156-168 patients. Patients will be treated until disease progression (as determined by RECIST v1.1 criteria evaluated every 8 weeks from first dose of study drug), toxicity, or physician or patient's choice (see Section 5.3).	**4 Enrollment and Treatment** Approximately 54 patients will be enrolled in Part 1. An additional 150 patients (50 patients per arm) will be enrolled during Part 2. Therefore, the total enrollment for the study will be approximately 204 patients. All patients will be treated until disease progression (as determined by RECIST v1.1 criteria evaluated every 8 weeks from first dose of study drug), unacceptable drug related toxicity, or physician or patient's choice (see Section 5.3).
13-14 &	Synopsis &		*Inclusion criteria a), b), c) and d) were modified based on the learnings of three completed dose level cohorts and inclusion*

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42-43	5.1	**5.1 Inclusion Criteria** a) Pathologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting: b) Measurable or non-measurable disease as defined by RECIST v1.1 c) ECOG performance status of 0 or 1 d) Adequate biological parameters as evidenced by the following blood counts: • ANC > 1,500 cells/µl without the use of hematopoietic growth factors, • Platelet count > 100,000 cells/µl, and • Hemoglobin > 9 g/dL j) Agreeable to submit unstained archived tumor tissue for analysis, if available	*criteria j) was removed (no changes were made to other inclusion criteria).* **5.1 Inclusion Criteria** a) Histologically or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting: b) At least one tumor lesion measurable by CT or MRI scan (according to RECIST v1.1 criteria) c) ECOG performance status of 0 or 1 at both Screening and within 72 hours prior to randomization. Two observers will be required to assess ECOG. If different, the lowest assessment will be used for the eligibility evaluation at each assessment d) Adequate biological parameters as evidenced by all of the following blood counts: • ANC > 1,500 cells/µl without the use of hematopoietic growth factors within last 7 days prior to Screening • Platelet count > 100,000 cells/µl • Hemoglobin > 9 g/dL; transfusion is allowed, provided interval is ≥ 7 days prior to Screening
14-15 & 43-44	Synopsis & 5.2	**5.2 Exclusion Criteria** a) Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed) b) Prior treatment of pancreatic cancer with cytotoxic doses of chemotherapy (patients receiving prior treatment with chemotherapy as a radiation sensitizer are	*Existing exclusion criteria a), b) and k) were modified and new exclusion criteria o), p) and q) were added based on the completion of previous 3 dose level cohorts (no changes were made to other exclusion criteria).* **5.2 Exclusion Criteria** a) Prior treatment of pancreatic cancer in the metastatic setting (or locally advanced setting, Part 1 only) with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed) b) Prior treatment of pancreatic cancer with cytotoxic doses of systemic anti-tumor therapy (patients receiving prior treatment

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		eligible if ≥ 6 months has elapsed from completion of therapy) k) Presence of any contraindications for 5-FU, leucovorin, or oxaliplatin	with chemotherapy as a radiation sensitizer are eligible if ≥ 6 months has elapsed from completion of therapy) k) Presence of any contraindications for 5-FU, leucovorin, oxaliplatin, gemcitabine or nab-paclitaxel o) Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma p) Documented serum albumin <3 g/dL at Screening Visit and within 72 hours prior to enrollment/ randomization (both labs at screening and prior to enrollment/randomization may be confirmed locally) q) Patients 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
44-45	5.3	**5.3 Patient Discontinuation** A patient may withdraw from the study at any time and for any reason. It is intended that patients will be treated until Investigator-determined progressive disease per RECIST v1.1 or unacceptable toxicity. Some possible reasons for early discontinuation of study treatment include, but are not limited to the following: • Progressive neoplastic disease per RECIST v1.1 • The patient experiences an adverse event which: o in the opinion of the Investigator, precludes further participation in the trial o requires treatment to be withheld for more than 14 days, unless in the opinion of the investigator the patient is receiving benefit from the study treatment o requires more than 2 dose reductions • Clinical and/or symptomatic deterioration	*Section 5.3 (Patient Discontinuation) was divided into Sections 5.3.1, 5.3.2 and 5.3.3.* **5.3 Patient Discontinuation** **5.3.1 Discontinuation of Study Treatment** It is intended that patients will be treated until radiologically determined progressive disease per RECIST v1.1 or unacceptable study drug related toxicity. However, a patient 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 v1.1 • Clinical deterioration sufficient to prevent further radiological assessment • A study drug related adverse event, prior to disease progression, which: o in the opinion of the Investigator, precludes further treatment with all study drugs o requires treatment with one or more study drugs to be withheld for more than 14 days, unless in the opinion

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		• Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial • Significant noncompliance with the protocol per PI assessment • Withdrawal of consent • The Investigator removes the patient from the trial in the best interests of the patient • Study termination by the Sponsor • Use of prohibited concomitant medications • Patient is lost to follow up If a patient withdraws from the trial, a complete final evaluation at the time of the patient's withdrawal should be made with an explanation of the reason for withdrawal. Following treatment discontinuation for other reasons above, all procedures and evaluations required at the 30 day follow up visit should be completed. All patients who discontinue the trial as a result of an adverse event must be followed until resolution or stabilization of the adverse event. Overall survival follow-up contacts should continue every 2 months from the 30-day follow-up visit until death or study closure, whichever comes first. If a patient does not return to the clinic for follow-up visits, attempts should be made to contact the patient via phone, email, or mail. At least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient is considered lost to follow-up, the date of death may be captured from public records.	of the investigator the patient is receiving benefit overall from the study treatment ○ would result in a third dose reduction in any single study drug (in a patient having already experienced 2 previous dose reductions) ○ requires discontinuation of nal-IRI (Arm I only) • Development of an intercurrent medical condition or need for concomitant therapy that precludes further treatment with all study drugs • Withdrawal of consent for further treatment • Pregnancy A patient who discontinues study medication has **not** withdrawn from the study and must continue with all ongoing protocol requirements, as detailed in Section 5.3.3. **5.3.2 Withdrawal from the Study)** A patient may withdraw, or be withdrawn, from the study at any time. Reasons for withdrawal from the study include, but are not limited to the following: • Significant noncompliance with the protocol, per Investigator's assessment • The Investigator removes the patient from the trial in the best interests of the patient • Use of prohibited concomitant medications • Patient is lost to follow up • Withdrawal of consent for further participation in the study • Death • Study termination by the Sponsor

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			5.3.3 Procedures following Study Drug Discontinuation or Study Withdrawal Following study drug discontinuation all procedures and evaluations required at the 30-day (End of Treatment) follow up visit should be completed. All patients who discontinue study medication as a result of an adverse event must be followed until resolution or stabilization of the adverse event. Patients who discontinue study drug 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 v1.1 has been documented. Overall survival follow-up contacts should continue every 2 months from the 30-day follow-up visit until death or study closure, whichever comes first. If a patient does not return to the clinic for follow-up visits, attempts should be made to contact the patient via phone, email, or mail. At least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient is considered lost to follow-up, the date of death may be captured from public records. If a patient withdraws from the study at any point, a complete final evaluation at the time of the patient's withdrawal should be made with an explanation of the reason for withdrawal. At the time of withdrawal from the study, it should be clarified with the patient whether they still consent to be followed up for survival status only (including where appropriate through publicly available records) and any such consent to ongoing survival follow up must be documented in both the source hospital records and the eCRF.
48	6.2.3	**6.2.3 Packaging and Labelling of Combination Therapies**	**6.2.3 Packaging and Labelling of Combination Therapies**

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		Commercially available 5-FU and leucovorin (*l* + d racemic form, or the levo-leucovorin *l* form), oxaliplatin, nab-Paclitaxel, and gemcitabine will be provided to enrolled patients in accordance with the specific treatment regimen in the respective arms. All patients who are enrolled to Arms 1 and 2 will be provided with 5-FU, leucovorin, and oxaliplatin, if applicable. All patients who are enrolled to Arm 3 will be provided with nab-Paclitaxel and gemcitabine, if applicable.	Sites participating in this protocol will source their own combination therapy supplies. However, for sites where this is not possible due to country legal or regulatory restrictions, Ipsen will provide commercially available 5-FU and leucovorin, oxaliplatin, nab-paclitaxel and gemcitabine as required by their enrolled patients for their specific treatment regimen. Ipsen sourced combination therapy supplies will be labeled in accordance with local regulatory requirements, and site accountability for all Ipsen sourced clinical trial material is required.
Through out	Synopsis, 3.1, 3.2.2 6.5.2 7.3.4 8	Patients will be tested for UGT1A1*28 status during screening, however the result of the test is not required prior to the initial dose of nal-IRI. For Part 1 patients receiving 80 mg/m^2 of nal-IRI: depending on the overall safety profile seen after the first dose, the dose may be reduced to 60 mg/m^2 after discussion between the PI, Sponsor and Medical Monitor. Any Part 1 patients who receive a reduced dose during Cycle 1 due to UGT1A1*28 homozygosity will not be evaluable for the cohort and will be replaced. For Part 2, UGT1A1*28 7/7 homozygous and non-homozygous genotype patients should receive the full	*Patients will be tested for UGT1A1*28 status during screening as a safety biomarker to further analyze the association between UGT1A1*28 homozygosity, SN-38 concentration and toxicity. However, the protocol does not contain formal recommendations on nal-IRI dose modifications as a consequence of homozygosity. The results of testing are not required prior to the first dose of nal-IRI but will be made available for review in Part 1 and the starting dose for all patients in Part 1 will be as per the dosing table (regardless of UGT1A1*28).* As part of this study, pharmacogenomic data will be collected on all patients for determination of UGT1A1*28 status. Importantly however, no grade 4 neutropenia was observed in patients homozygous for the wild-type (WT) 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 [25]). Population PK studies of nal-IRI have not identified a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure (see Investigator Brochure). In a Phase I study (UCSF 8603, as referenced in Table 2 above) no differences in toxicity were seen in cohorts of heterozygous or WT patients,

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		starting dose of nal-IRI; All Arm 1 subjects should start at 60 mg/m^2, while all Arm 2 patients will begin dosing at 80 mg/m^2. Follow the tables above for guidance on dose modification due to toxicity.	and DLTs of diarrhea with or without accompanying dehydration or fatigue, were seen in both cohorts. Because of these discrepancies in the severity of previously documented toxicity arising from UGT1A1*28 homozygosity, and because the prevalence of UGT1A1*28 homozygosity is relatively low, testing results will not be required prior to the first dose of nal-IRI on this study and the starting dose for all patients in Part 1 will be as described in Table 5. The protocol does not contain formal recommendations on nal-IRI dose modifications as a consequence of homozygosity. All patients should receive the full starting dose of nal-IRI. All Arm 1 patients should start at the dose level identified from Part 1, while all Arm 2 patients will begin dosing at 80 mg/m^2. The UGT1A1*28 status of each patient will subsequently be made available to individual investigators.
59	6.5.5	**6.5.5 Rules for Dose Omissions and Modified Schedules** The following guidance should be followed when all study drugs in any arm are held/missed: • If Day 1 doses are held/missed: the doses intended for Day 1 of a cycle should be delayed, such that the start of that cycle will not begin until the doses are actually administered to the patient • If Day 8 doses are held/missed (applies to Arm 3 only): the cycle will continue per protocol and those doses will be considered missed. • If Day 15 doses are held/missed: o **Arms 1 and 2 only:** if toxicity recovers within 7 days, the day 15 doses may be delayed and subsequently given 1 week late. The next cycle would then continue 14 days following the administration of the delayed Day 15 dose.	**6.5.5 Rules for Dose Omissions and Modified Schedules** The following guidance should be followed when all study drugs in any arm are held/missed: For both Part 1 and Part 2, the maximum delay between the date of a scheduled but missed dose and the planned next dose should be up to 14 days. In Part 2, Arm 3, • If Day 1 doses are held/missed: the doses intended for Day 1 of a cycle should be delayed, such that the start of that cycle will not begin until the doses are actually administered to the patient • If Day 8 doses are held/missed: the cycle will continue per protocol and those doses will be considered missed. • If Day 15 doses are held/missed: the dose will be considered missed and dosing will continue with Day 1 of the next cycle when toxicity recovers.

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		However, if the toxicity recovers between 7-14 days after scheduled Day 15 dose (i.e. dose is delayed for 2 weeks), that dose will be considered missed and Day 1 of the next cycle should occur as originally scheduled. ○ **Arm 3 only:** the dose will be considered missed and dosing will continue with Day 1 of the next cycle when toxicity recovers (e.g. if toxicity recovers within 7 days, that week will be considered the rest week, and the next cycle can begin 1 week after the previously scheduled Day 15 dose; alternatively, if the toxicity recovers between 7-14 days from the scheduled Day 15 dose, the Day 1 dose of the next cycle should occur as originally scheduled).	
63, 67-69 90	7.2.3, 8 & Appendix 3	Only ECOG performance status to be recorded at Screening and within 72 hours of enrolment/randomization	*In additional to the ECOG performance status, KPS was also to be recorded at Screening and within 72 hours of enrolment/randomization.* *An additional Appendix 3 was added for evaluating the KPS.*
81-82	12.9	As the Study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication report has been submitted for publication in a peer reviewed journal within twelve (12) months of the completion of this Study at all sites, the Investigator shall have the right to publish or present independently the results of this	*Publication policy was updated as per Ipsen Bioscience standards:* The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor. The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee. The sponsor

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		patient to the review procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least forty-five (45) days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed ninety (90) days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights. The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the Collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s). The Sponsor or its designee has the right at any time to publish the results of the Study.	requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material. 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. 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.
84-85	13		*Five new references were added to the reference list.* [28] R.W. Marsh, M.S. Talamonti, M.H. Katz and J.M. Herman, "Pancreatic cancer and FOLFIRINOX: a new era and new questions," Cancer Med., vol. 4, no. 6, pp. 853–863, Jun 2015.

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			[29] B. Chibaudel, F. Maindrault-Goebel, J.B. Bachet, C. Louvet, A. Zhalil, O. Dupuis, P. Hammel, M-L. Garcia, M. Bennamoun, D. Brusquant, C. Tournigand, T. André, C. Arbaud, A.K. Larsen, Y-W. Wang, C.G. Yeh, F. Bonnetain and A de Gramont, "PEPCOL: a GERCOR randomized phase II study of nanoliposomal irinotecan PEP02 (MM-398) or irinotecan with leucovorin/5-fluorouracil as second-line therapy in metastatic colorectal cancer," Cancer Med. vol. 5, no. 4, pp. 676-683, Apr. 2016. [32] T.J. Smith, K. Bohlke, G.H. Lymann, K.R. Carson, J. Crawford, S.J. Cross, J.M. Goldberg, J.L. Khatcheressian, N.B. Leighl, C.L. Perkins, G. Somlo, J.L Wade, A.J. Wozniak, American Society of Clinical oncology, "Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update," J Clin Oncol. Vol. 33, no. 28, pp. 3199-3212, Oct. 2015. [33] M.S. Aapro, J Bohlius, D.A. Cameron, L.D. Lago, J.P. Donnelly, N. Kearney, G.H. Lyman, R. Pettengell, V.C.Tjan-Heijnen, J. Walewski, D.C. Weber, C. Zielinski and European Organisation for Research and Treatment of Cancer "2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours," Eur J Cancer, vol. 47, no. 1, pp. 8 32, Jan. 2011. [34] J. Crawford, C. Caserta J, F. Roila; ESMA Guidelines Working Group, "Haematopoietic growth factors: ESMO Clinical Practice Guidelines. Ann Oncol, vol. 21 (Suppl 5), pp. v248-v251, May. 2010.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	MM-398-07-02-03	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Version 5.0, 29 September 2017**	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
OBJECTIVE(S) OF PROTOCOL AMENDMENT	5. To optimize the NAPOX regime (irinotecan liposome injection + 5-FU/LV + oxaliplatin) in patients with metastatic pancreatic adenocarcinoma by assessing an additional dose for the combination regimen (Part 1A) 6. To expand the study sample size (Part 1B), once the dose is selected from Part 1A, to further evaluate the safety and efficacy signals and update the study design accordingly 7. To adjust the inclusion and exclusion criteria based on learnings from the three completed dose level cohorts.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐ *(tick one)*

Appendix 7: Summary of Changes: 29 September 2017 (version 5.0) to 11 April 2018 (version 6.0)

STUDY NUMBER:	MM-398-07-02-03
PROTOCOL TITLE:	**A RANDOMIZED, OPEN-LABEL PHASE 2 STUDY OF NANOLIPOSOMAL IRINOTECAN (NAL-IRI)-CONTAINING REGIMENS *VERSUS* NAB-PACLITAXEL PLUS GEMCITABINE IN PATIENTS WITH PREVIOUSLY UNTREATED, METASTATIC PANCREATIC ADENOCARCINOMA**
AMENDED PROTOCOL VERSION NUMBER & DATE	Version 6.0, 11 April 2018

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED: Minor formatting, typos and rephrasing of text to enhance clarity have not been recorded. Underlined text in "Was" indicates deleted text; Bold text in "Is" indicates new text. This does not apply to tables.

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Throughout	Synopsis,1.1.1, 1.3, all 2, all 3, 4, 4.1, 4.2, 5.1, 5.2, 5.3.1, 6.1.1.3, all 6.2, all 6.3, 6.4, all 6.5, 6.7, 7.1.2, 7.2.4, 7.2.7, 7.3.7, 8, 10.4-10.10	*The study is divided into two parts: Part 1 and 2.*	*Part 2, which consisted in a comparison of nal-IRI-containing regimens versus nab-paclitaxel plus gemcitabine, has been removed. Consequently, all mentions of Part 1, Part 2, nab-paclitaxel + gemcitabine and nal-IRI + 5-FU/LV (Arms 1 to 3 (the use of Arm 1 was reserved for use in the context of Part 2 only)) have been deleted.* *These changes are general and not described systematically in the below list of changes.* *Only Parts 1A and 1B remain unchanged.*
7	Summary of changes	The current version of the protocol (Version 5.0) was released on 29 September 2017. This amendment brings together two previous amendments into the single protocol version 5.0. The summary and outcome of changes are presented in: • Appendix 6: Summary of Changes 28 December 2016 (Version 3.1) to 29 September 2017 (Version 5.0	The current version of the protocol (Version 6.0) was released on 11 April 2018. **This protocol version includes all amendments, with summaries of changes from Version 3.1 included in the following appendices. The main purposes of this amendment are to remove Part 2 of the study and all related information, add inclusion**

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		• Appendix 7: Summary of Changes: 03 April 2017 (Version 4.0) to 29 September 2017 (Version 5.0). The changes for both amendments were substantial	**and exclusion criteria and some clarifications (see Appendix 7).** • Appendix **5**: Summary of Changes 28 December 2016 (Version 3.1) to 29 September 2017 (Version 5.0) • Appendix **6**: Summary of Changes: 03 April 2017 (Version 4.0) to 29 September 2017 (Version 5.0). • **Appendix 7: Summary of Changes 29 September 2017 (Version 5.0) to 11 April 2018 (Version 6.0)** The changes for **all** these amendments were substantial.
9	Abbreviations		**UDP: Uridine diphosphate** **UGT: UDP-glucuronosyltransferase**
10	Synopsis	Rationale Two combination chemotherapy regimens have emerged as standard of care options for first-line treatment of metastatic pancreatic cancer: 5-fluorouricil (5 FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX), and nab-paclitaxel + gemcitabine, demonstrating a median overall survival (OS) of 11.1 months and 8.5 months, respectively, in separate Phase 3 studies. Nal-IRI (also known as MM 398) is a nanoliposomal formulation designed to deliver irinotecan to the tumor microenvironment for local drug activation. In a randomized phase 3 study, patients with metastatic pancreatic cancer who had progressed on gemcitabine alone (the NAPOLI-1 study), nal-IRI in combination with 5-FU/LV demonstrated significant clinical activity, increasing OS and progression free survival (PFS) relative to 5 FU/LV. The goal of this current study is to assess the preliminary efficacy and safety of nal-IRI-containing regimens, including nal-IRI + 5-FU/LV + oxaliplatin and nal-IRI + 5-FU/LV, in previously untreated	Rationale Nal-IRI (also known as MM 398) is a nanoliposomal formulation designed to deliver irinotecan to the tumor microenvironment for local drug activation. In a randomized phase 3 study, patients with metastatic pancreatic cancer who had progressed **following gemcitabine-based therapy** (the NAPOLI-1 study), nal-IRI in combination with 5-FU/LV demonstrated significant clinical activity, increasing OS and progression free survival (PFS) relative to 5 FU/LV. The goal of this current study is to assess the safety, **tolerability** and preliminary efficacy of nal-IRI **in combination with** 5-FU/LV and oxaliplatin in **patients not** previously **treated for** metastatic pancreatic **adenocarcinoma** to select **a** regimen for further development.

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		metastatic pancreatic cancer patients to select the regimen for further development.	
11	Synopsis	Protocol Version 5.0 Update: The original plan in the study was to evaluate dose levels in Part 1 as described in the table above. Dose level cohorts 1, -1 and -2B have been evaluated. Dose levels 1 and -2B were considered to be not tolerable. Dose level -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable. Following the completion of the three predefined dose level cohorts, this protocol amendment introduces a new dose level -3 (oxaliplatin 70 mg/m2 + nal-IRI 65 mg/m2) for evaluation. Dose levels 2 and -2A will not be evaluated in the study.	The original plan in the study was to evaluate dose levels as described in the table above. Dose level cohorts 1, -1 and -2B have been evaluated. Dose levels 1 and -2B were considered to be not tolerable. Dose level -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable. Following the completion of the three predefined dose level cohorts, a new dose level -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) **was introduced following a protocol amendment (protocol Version 5.0) to evaluate its safety and tolerability.** Dose levels 2 and -2A **were considered** not **to** be evaluated in the study. **Prior to this Version 5.0, the enrollment of dose level cohorts 1, -1 and -2B had been completed.**
16	Synopsis	Length of Study All patients in Part 1 and Part 2 will be treated until disease progression, intolerable toxicity, or at the discretion of the treating physician. A follow up clinic visit is required approximately 30 days after last dose of study treatment to complete the final safety assessments. Subsequently, patients will be followed for survival once every 2 months via telephone, email, or clinic visit until death, or study closure, whichever occurs first.	Length of Study All patients **in the study** will be treated until disease progression, **unacceptable drug related** toxicity, or physician **or patient's choice**. A follow up clinic visit is required approximately 30 days after last dose of study treatment to complete the final safety assessments. Subsequently, patients will be followed for survival once every 2 months via telephone, email, or clinic visit until death, **lost to follow-up, withdrawal of consent**, or study closure, whichever occurs first.
16	Synopsis	Dosing regimens All regimens below will be tested in 28-day cycles, unless cycle duration is modified by toxicity in accordance with Section 6.5.5. Part 2: Arm 1: nal-IRI + 5-FU/LV + oxaliplatin	Dosing regimen **The regimen** below will be tested in 28-day cycles, unless cycle duration is modified by toxicity in accordance with Section **6.5.3**. If oxaliplatin is not well tolerated, oxaliplatin may be discontinued and patients may continue to receive nal-IRI + 5-FU/LV at the discretion of the Investigator. Toxicity

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		• Oxaliplatin will be administered at a dose level identified from Part 1, IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle • Nal-IRI will be administered at a dose level identified from Part 1 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. • 5-FU will be administered 2400 mg/m2 IV over 46-hours (±60 minutes), on Days 1 and 15 of each 28-day cycle • Leucovorin (l + d racemic form) 400 mg/m2, IV over 30 minutes (±5 minutes), on Days 1 and 15 of each 28-day cycle Note: The order of infusions on Arm 1 will be as follows: nal-IRI will be administered first, followed by oxaliplatin, then LV, followed by 5-FU. In Part 1, patients will receive the oxaliplatin infusion 2 hours after the completion of the nal IRI infusion and will receive leucovorin 30 min after oxaliplatin. If no infusion reactions are seen, Part 2 patients can receive oxaliplatin directly after completion of the nal-IRI infusion and leucovorin directly after completion of oxaliplatin (see Section 6.3.1 for details). If oxaliplatin is not well tolerated in patients enrolled in Arm 1, oxaliplatin may be discontinued and patients may continue to receive nal-IRI + 5-FU/LV at the discretion of the Investigator. Toxicity requiring discontinuation of nal-IRI will result in discontinuation from all study treatments. Arm 2: nal-IRI + 5-FU/LV The dose and regimen that is planned for Arm 2 has been previously studied in 117 patients who participated in the NAPOLI-1 trial, therefore a safety cohort in Part 1 is not	requiring discontinuation of nal-IRI will result in discontinuation from all study treatments.

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		needed. The following doses will be administered in Part 2 of the study: • nal-IRI 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle • 5-FU 2400 mg/m^2 IV over 46-hours (±60 minutes), on Days 1 and 15 of each 28-day cycle • leucovorin l + d racemic form 400 mg/m^2, IV over 30 minutes (±5 minutes), on Days 1 and 15 of each 28-day cycle Patients will be tested for UGT1A1*28 status during screening. However, the protocol does not contain formal recommendations on nal-IRI dose modifications as a consequence of homozygosity. The results of testing are not required prior to the initial dose of nal-IRI but will be made available for review in Part 1. For Part 2, all patients should receive the full starting dose of nal-IRI; all Arm 1 patients should start at the dose level identified from Part 1, while all Arm 2 patients will begin dosing at 80 mg/m^2. The UGT1A1*28 status of each patient will subsequently be available to individual investigators, if judged clinically necessary by the investigator. **Arm 3: nab-paclitaxel + gemcitabine** • nab-paclitaxel 125 mg/m^2 IV over 35 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle gemcitabine 1000 mg/m^2 IV over 30 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle	

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17	Synopsis	Criteria for evaluation: Plasma samples will be analyzed for the concentration of nal-IRI (irinotecan) and its metabolites (SN-38 and SN-38G) in order to derive PK parameters of nal-IRI when given in combination with other anticancer therapies. PK parameters of the combination therapies (5-FU and oxaliplatin) will also be analyzed to evaluate any drug interactions with nal-IRI. Efficacy in Part 1: Efficacy in Part 1 will be analyzed descriptively. Efficacy parameters summarized will include DCR at 16 weeks, duration of response, ORR, PFS and OS. Part 2 The primary endpoint is PFS, which will be assessed in all 3 study arms. The secondary endpoints related to efficacy will include median OS and overall response (CR or PR, per RECIST, v 1.1). Achievement of a 20%/50%/90% or greater decrease in CA19-9 levels compared to baseline (at 8, 16, and 24 weeks post treatment and overall) will also be assessed, along with a quality of life assessment (EORTC-QLQ-C30 and EQ-5D-5L). QTcF prolongation will be assessed in the Arm 2 (nal-IRI+5-FU/LV) in patients with PK and QTcF measurements. Translational / Exploratory Archived tumor tissue (if available) and blood samples will be collected and analyzed for biomarkers (Parts 1 and 2). Samples will be used to explore potential markers of sensitivity and resistance to irinotecan, including, but not limited to, the following: DNA damage repair pathways (e.g. Topo1, BRCA1/2, and SLFN11), growth factor pathways (IGF1 and EGFR family receptors and ligands),	Criteria for evaluation: **Pharmacokinetic evaluation:** Plasma samples will be analyzed for the concentration of nal-IRI (irinotecan) and its **metabolite** (SN-38) in order to derive PK parameters of nal-IRI when given in combination with other anticancer therapies. PK parameters of the combination therapies (5-FU and oxaliplatin) will also be **determined, where warranted by the data,** to evaluate any drug interactions with nal-IRI. Efficacy **evaluation:** **Preliminary** efficacy will be analyzed descriptively. Efficacy parameters summarized will include DCR at 16 weeks, duration of response, ORR, PFS and OS. Translational / Exploratory Archived tumor tissue (if available) and blood samples will be collected and analyzed for biomarkers. Samples will be used to explore potential markers of sensitivity and resistance to irinotecan, **which may include**, but are not limited to, the following: **Topoisomerase-1**, growth factor pathways (IGF1 and EGFR family receptors and ligands), and factors involved in CPT-11 conversion to SN-38.

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		and factors involved in CPT-11 conversion to SN-38 (e.g. macrophage content and CES activity).	
18	Synopsis	Pharmacokinetic analyses **Part 1 and Part 2 Arm 1** Plasma concentrations of total irinotecan, SN-38, and oxaliplatin in the combination therapies will be used to characterize PK parameters. PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method with priors from the previously published parameters. The model simulated exposures, e.g., C_{max}, AUC (area under the curve), will be compared in order to examine any possible interactions between nal-IRI and the combination therapies and to evaluate the relationship between dose, PK, efficacy and safety endpoints. **Part 2 Arm 2** Plasma concentrations of total irinotecan, SN-38 and 5-FU will be characterized based on the Empirical Bayesian Estimation method with priors from previously published parameters. The relationship between dose, PK, efficacy and safety endpoints will be evaluated. Moreover, the relationship between PK and QTcF will be used to evaluate the potential for QTcF prolongation (see below). **QTcF Analyses** The potential for QTcF prolongation with nal-IRI treatment will be evaluated in patients in Arm 2, Part 2 of this study. For the primary QTcF prolongation analysis, the predicted changes in QTcF will be obtained from the exposure-QTcF relationship using mixed-effect modeling. Sensitivity analyses will be conducted by evaluating by-timepoint and categorical analyses.	Plasma concentrations of total irinotecan, SN-38, oxaliplatin and **5-FU** in the combination therapies will be used to characterize **corresponding** PK parameters **using a nonlinear mixed effects approach**. **Individual** PK parameters will be estimated **if warranted by the data**. **Graphical exploration will be performed to investigate** any relationship between PK and **pharmacodynamic** endpoints. **If a trend is shown, PK/PD modelling will be performed and reported separately.**

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20; 29	1.1.1, 1.3	Nal-IRI, a liposomal formulation of irinotecan, has recently been studied in a randomized, Phase 3, international study (NAPOLI-1), in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapy, in which the combination of nal-IRI and 5-FU/LV significantly prolonged OS compared to 5-FU/LV treatment alone, in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapy [9].	Nal-IRI, a liposomal formulation of irinotecan, has recently been studied in a randomized, Phase 3, international study (NAPOLI-1), in which the combination of nal-IRI 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 [9].
20, 29	1.1.1, 1.3	The goal of the present study is to assess the efficacy and safety of nal-IRI, in combination with other anticancer therapies (i.e. 5-FU/LV and/or oxaliplatin) in previously untreated metastatic pancreatic cancer patients, compared to a nab-paclitaxel + gemcitabine control arm.	The goal of the present study is to assess the **safety, tolerability and preliminary** efficacy of nal-IRI, in combination with 5-FU/LV and oxaliplatin in **patients not previously treated for** metastatic pancreatic **adenocarcinoma**.
21	1.1.1.3	**Description of Gemcitabine** Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor 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 package insert for more details [13]). 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.	*Deleted text*
21	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 stabilizes microtubules by preventing depolymerization. Paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters	*Deleted text*

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		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 package insert for more details [14]).	
22	1.2.2	Nine clinical studies of nal-IRI have been completed to date, with over 400 patients across multiple tumor types exposed to various dosing regimens, with an additional four studies actively recruiting patients across multiple tumor types	Clinical studies of nal-IRI have been completed, with over 400 patients across multiple tumor types exposed to various dosing regimens, with additional studies actively recruiting patients across multiple tumor types *Foot-notes of Tables 1 and 2 have been updated with their creation date:* **Date: 28 December 2016**
29	1.3	1.3.1 Rationale for Arm 1: Nal-IRI + 5-FU/LV + Oxaliplatin	1.3.1 Rationale for Nal-IRI + 5-FU/LV + Oxaliplatin
30-32	1.3	1.3.2 Rationale for Arm 2: Nal-IRI + 5-FU/LV Tolerability of multi-drug regimens is important in advanced cancer. The longer the duration of manageable treatment should translate into improved outcome due to longer drug exposure. Triplet drug regimens such as FOLFIRINOX are known to have significant toxicity, and use is limited to patients with better performance status (i.e. ECOG performance score of 0 or 1). With prolonged FOLFIRINOX treatment, oxaliplatin is often discontinued from the regimen due to toxicity. Therefore, if equally effective doublet regimens can be identified, patients may be able to tolerate prolonged treatment better, and even poor performance status patients may receive benefit. Given the statistically significant improvement of OS of the nal-IRI + 5-FU/LV doublet in patients with metastatic pancreatic cancer previously treated with gemcitabine in the NAPOLI-	1.3.2 **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. UGT1A1*28 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 Camptosar® (nonliposomal irinotecan). Multiple studies have evaluated the association between**

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<tr><td></td><td></td><td>1 trial [11], [26], it is logical to test this combination in previously untreated metastatic pancreatic cancer. As suggested by the pre-clinical data (shown in Figure 4, above), it is possible that the advantages of the liposomal formulation of nal-IRI result in a more effective doublet, such that the addition of oxaliplatin may not be necessary to significantly impact tumor response. In this case, it may be possible to spare patients additional toxicity that would be expected with the addition of oxaliplatin. Table 5 below summarizes the efficacy and safety results of the NAPOLI-1 trial compared with two standard of care options for first-line metastatic disease. Although this is a cross-study comparison, the nal-IRI + 5-FU/LV doublet regimen may have a safety advantage over either FOLFIRINOX or nab-paclitaxel + gemcitabine with respect to both neutropenia and neuropathy.

Table 5: Comparison of Efficacy and Safety Characteristics of nal-IRI + 5-FU/LV versus 2 Standard of Care Regimens

<table>
<tr><th>Regimens</th><th>Nal-IRI + 5FU-LV[a]</th><th>FOLFIRINOX[b]</th><th>Nab-paclitaxel + gemcitabine +[c]</th></tr>
<tr><td>Setting</td><td>Post-gemcitabine</td><td colspan="2">Front-line Metastatic Disease</td></tr>
<tr><td>Efficacy</td><td></td><td></td><td></td></tr>
<tr><td>Hazard Ratio</td><td>0.57</td><td>0.57</td><td>0.72</td></tr>
<tr><td>Median Overall Survival</td><td>6.1 months</td><td>11.1 months</td><td>8.5 months</td></tr>
<tr><td>Change vs. Control</td><td>1.9 months</td><td>4.3 months</td><td>1.8 months</td></tr>
<tr><td>Adverse Events ≥ Grade 3</td><td></td><td></td><td></td></tr>
</table></td><td>UGT1A1*28 7/7 homozygosity, SN-38 concentration and safety in patients treated with Camptosar® 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 15-75 mg/m^2 daily for 5 days for 2 consecutive weeks (41-159% vs. 10-40%, respectively) [27] [28]. In a study of 66 patients who received single-agent non-liposomal irinotecan (350 mg/m^2 every 3 weeks), the incidence of Grade 4 neutropenia in patients heterozygous (UGT1A1*28 6/7) and homozygous (7/7) for the UGT1A1*28 was 12.5% and up to 50% respectively (Camptosar® USPI). In a subsequent study, association between UGT1A1*28 homozygosity and hematological toxicity was observed only in patients treated with >150 mg/m^2 non-liposomal irinotecan. By contrast, at lower dose of non-liposomal irinotecan (100-125 mg/m^2 every week) similar hematological toxicities were observed for both homozygous and non-homozygous patients [29]. 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 [30].

In patients treated with irinotecan liposome injection, the association between UGT1A1*28 homozygosity, SN-38, and hematologic toxicity is primarily obtained from study NAPOLI-1, where UGT1A1*28 homozygous patients were treated at reduced dose (50 vs 70 mg/m^2</td></tr>
</table>

Neutropenia	20%	45%	38%
Febrile neutropenia	2%	5%	3%
Fatigue	14%	24%	17%
Vomiting	11%	15%	<5%
Diarrhea	13%	13%	6%
Neuropathy	None	9%	17%

[a] Data from Phase 3 trial of nal-IRI + 5-FU/LV vs. 5-FU/LV [11]
[b] Data from Phase 3 trial of FOLFIRNOX vs. gemcitabine [1]
[c] Data from Phase 3 trial of nab-paclitaxel + gemcitabine vs. gemcitabine [2]

every 2 weeks in combination with 5-FU/LV, or 70 vs. 100 mg/m^2 every 3 weeks monotherapy). The evaluation of the association between SN-38 concentration and UGT1A1*28 homozygosity was performed only for Caucasians, because homozygosity was rare in Asians (2/129; 1.5%). Based on the population PK and exposure-response analysis, similar un-encapsulated SN-38 C_{max} values were observed for homozygous and non-homozygous Caucasian patients if both are dosed at 70 mg/m^2 (1.99 [95% CI 1.81-2.18, n=12] and 1.76 [95% CI 1.69-1.84, n=141] ng/mL; p=0.66; both of these values are approximately half of the expected SN-38 C_{max} from a 120 mg/m^2 dose of non-liposomal irinotecan). Consequently, the predicted grade 3 or higher neutropenia was also similar if treated at 70 mg/m^2 monotherapy (8.7% vs. 7.4%, respectively), or if treated at 90 mg/m^2 monotherapy (15% vs. 13%, respectively). Additionally, in a phase I study (UCSF 8603), no differences in toxicity were seen in cohorts of UGT1A1*28 6/7 (n=18) or 6/6 (n=16) patients, 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 hematological toxicity appear to depend on the incoming load of SN-38 to be metabolized 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

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			appears to spread out the incoming load of SN-38 by controlling the release of irinotecan. This is supported by a study in patients 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) [31]. 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 US package insert 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 patients as a safety biomarker to further analyze the association between UGT1A1*228 homozygosity, SN-38 concentration and toxicity. Irinotecan liposome injection dose reduction will follow the same dose reduction rules for all patients regardless of UGT1A1*28 genotype. Patients with UGT1A1*28 homozygosity will be closely monitored for safety in comparison to the safety in patients with UGT1A1*28**

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			non-homozygous status by the medical monitors of the sponsor and by the DLT committee.
30-32	1.3	1.3.3 Rationale for Arm 3: Nab-paclitaxel + Gemcitabine Control Arm 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 combination became a preferred first-line treatment option according to the NCCN recommendations in 2013 [27]. In a Phase 3, international study of 861 patients (MPACT trial), nab-paclitaxel + gemcitabine demonstrated a mOS of 8.5 months versus 6.7 months for gemcitabine alone (HR 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001) [2]. While nab-paclitaxel + gemcitabine is generally thought to be more tolerable than FOLFIRINOX, this combination is associated with neuropathy and neutropenia, and has not been compared directly with FOLFIRINOX (see Table 5). In the current study, the nab-paclitaxel + gemcitabine regimen will be compared to nal-IRI-containing regimens, including the modified triplet regimen which substitutes nal-IRI instead of irinotecan.	*Deleted text*
10, 32	Synopsis, 2.1	The study is divided into two parts: Part 1 **Primary objectives:** • To characterize dose-limiting toxicities (DLTs) associated with nal-IRI + 5 FU/LV + oxaliplatin and determine the Part 2 dose of the triplet combination	**Primary objectives:** • To characterize dose-limiting toxicities (DLTs) associated with nal-IRI + 5 FU/LV + oxaliplatin and determine the **recommended** dose of the triplet combination **for future development**
10,	Synopsis,	Part 2:	*Deleted text*

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32	2.2	**Primary objectives:** • To assess the efficacy of nal-IRI-containing regimens in first-line metastatic pancreatic cancer patients compared to nab-paclitaxel + gemcitabine using progression free survival (PFS) **Secondary Objectives** • To assess efficacy of each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine using OS and ORR • To assess tumor marker CA19-9 response in each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine • To assess health-related quality of life (HRQL) using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30) and European Quality of Life Questionnaire (EQ-5D-5L) between the treatment arms • To compare the safety and adverse event profile between the treatment arms • To assess the potential for QTcF prolongation with nal-IRI treatment	
10, 32	Synopsis, 2.3	**Exploratory Objectives** • To evaluate the relationship between plasma PK of nal-IRI (total irinotecan, SN-38) oxaliplatin, and efficacy and safety endpoints in first-line metastatic pancreatic cancer • To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI, PK, toxicity, and/or response	**Exploratory Objectives** • To evaluate the relationship between plasma PK of nal-IRI (total irinotecan, SN-38) **in combination with 5-FU and oxaliplatin**, and safety and efficacy endpoints in first-line metastatic pancreatic cancer • To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI **in combination with 5-FU/LV and oxaliplatin,** PK, toxicity, and/or response
10-11,	Synopsis,	This is an open-label, Phase 2 comparative study to assess the safety, tolerability, and efficacy of nal-IRI in	This is an open-label, Phase 2 study to assess the safety, tolerability, and **preliminary** efficacy of nal-IRI in

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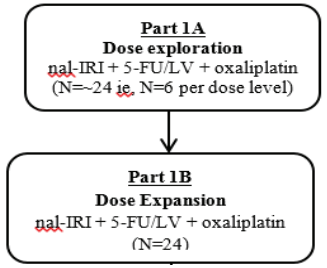
32-33	3.1	combination with other anticancer therapies, compared to nab-paclitaxel + gemcitabine, in patients with advanced pancreatic adenocarcinoma who have not received prior systemic anti-tumor therapy. The study will be conducted in two parts, as illustrated in the schematic below: 1) an initial dose exploration (Part 1A) followed by dose expansion (Part 1B) of the nal-IRI + 5-FU/LV + oxaliplatin regimen, and 2) a randomized, efficacy study of the nal-IRI + 5-FU/LV + oxaliplatin regimen (Part 2), the nal-IRI + 5-FU/LV combination that previously demonstrated efficacy in the Phase 3 NAPOLI-1 trial (i.e. the NAPOLI regimen), versus a nab-paclitaxel + gemcitabine control arm. This study will assess the following regimens in Part 2: • nal-IRI + 5-FU/LV + oxaliplatin (Arm 1) • nal-IRI + 5-FU/LV (Arm 2) • nab-paclitaxel + gemcitabine (Arm 3)	combination with 5-**FU/LV and oxaliplatin** in patients **not previously treated for metastatic** pancreatic adenocarcinoma. The study will be conducted, as illustrated in the schematic below, with an initial dose exploration (Part 1A) followed by dose expansion (Part 1B) of the nal-IRI + 5-FU/LV + oxaliplatin regimen. 

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		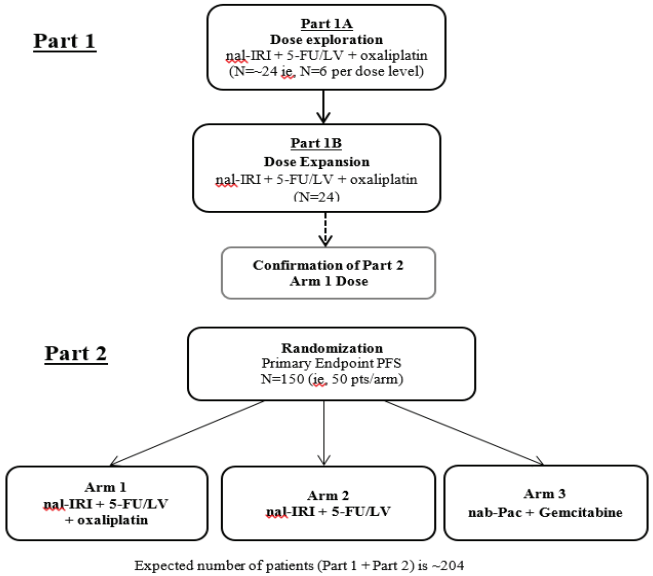 Part 1 will consist of an open-label dose exploration (Part 1A) followed by dose expansion (Part 1B) of the combination regimen to be used in Arm 1 of Part 2: nal-IRI + 5-FU/LV + oxaliplatin. The Arm 2 and Arm 3 of Part 2 regimens have established doses, and nal-IRI + 5-FU/LV has been demonstrated to be tolerable, yielding antitumor responses in a Phase 3 study of patients with relapsed metastatic pancreatic cancer, and therefore will not be included in this part of the study.	

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11, 33	Synopsis,3.1	In the absence of DLT, a minimum of 3 patients will be treated within each dose level cohort for a minimum of one cycle of therapy. Additional patients will be recruited into a cohort according to the DLT provisions outlined in Section 3.2.2, or if non-DLT toxicity is identified as requiring further evaluation by the DLT Committee (comprising the Part 1 Investigators, the Medical Monitor, and the Sponsor).	**Safety evaluations are to be conducted regularly by the DLT committee to review all SAEs, AEs and DLTs for each patient to determine the safety and tolerability in each Cohort. The DLT Committee is comprised of the Investigators, the Medical Monitor, and the Sponsor.** In the absence of DLT, a minimum of 3 patients will be treated within each dose level cohort for a minimum of one cycle of therapy. Additional patients will be recruited into a cohort according to the DLT provisions outlined in Section 3.2.2, or if non-DLT toxicity is identified as requiring further evaluation by the DLT Committee.
12, 33	Synopsis, 3.1, 4.1	If one DLT occurs within a given dose level cohort, then the cohort will be expanded to a minimum of 6 patients.	If one DLT occurs within **the first 3 patients in** a given dose level cohort, then the cohort will be expanded to a minimum of 6 patients.
34	3.1	This protocol amendment introduces a new dose level cohort in Part 1A (dose level -3: oxaliplatin 70 mg/m2 + nal-IRI 65 mg/m2) to evaluate its safety and tolerability. Prior to this amendment, the enrollment of dose level cohorts 1, -1 and -2B has been completed	**The protocol Version 5.0** introduced a new dose level cohort in Part 1A (dose level -3: oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) to evaluate its safety and tolerability, **following the completion** of the dose level cohorts 1, -1 and -2B.
12, 34	Synopsis, 3.1	At the completion of the safety evaluation period for dose level cohorts -1 to -3 (Part 1A) detailed in Table 6 all available data (DLT, SAE, and grade 3-4 adverse events, any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data) are reviewed by the DLT Committee.	At the completion of the safety evaluation period **(as defined in Section 3.2.2) for the last patient enrolled** for dose level cohorts -1 to -3 (Part 1A) detailed in Table 5, all available data (DLT, SAE, and grade 3-4 adverse events, any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data) are reviewed by the DLT Committee.

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12, 34	Synopsis, 3.1	Final determination of the Part 2 dose for Arm 1 will be made after all patients in the Part 1A (dose escalation) and Part 1B (expansion cohort) have completed two scheduled assessments (approximately 16 weeks of therapy; unless withdrawn at an earlier time point due to disease progression or drug-related toxicity). The DLT Committee will review all available data from the expansion cohort and also all available updated data for patients still receiving ongoing therapy in the other dose level cohorts.	Final determination of **an appropriate combination regimen for potential future development** will be made after all patients in the Part 1A (dose escalation) and Part 1B (expansion cohort) have completed two scheduled assessments (approximately 16 weeks of therapy; unless withdrawn at an earlier time point due to disease progression or drug-related **toxicity) and will take into account** all available data from the expansion cohort and also all available updated data for patients still receiving ongoing therapy in the other dose level cohorts.
34	3.1	Efficacy analysis (Part 1) will be performed when Week 16 DCR classifications can be made for all patients in Part 1. This should occur when all patients have either achieved disease control at 16 weeks (i.e. have no PD up to and including the Week 16 assessment with documented non-PD [SD, PR, or CR] assessment) or have discontinued from treatment (refer to Section 5.3 for study treatment discontinuation criteria). Further details on DCR analyses are presented in Section 10.6.	Efficacy analysis will be performed when Week 16 DCR classifications can be made for all patients. This should occur when all patients have either achieved disease control at 16 weeks (i.e. have no PD up to and including the Week 16 assessment with documented non-PD [SD, PR, or CR] assessment) or have discontinued from treatment (refer to Section 5.3 for study treatment discontinuation criteria). Further details on DCR analyses are presented in Section 10.6.
13; 34	Synopsis, 3.1	Part 2: Part 2 will consist of an open-label, randomized, Phase 2 study where patients will be randomized to treatment (1:1:1) to either nal-IRI + 5-FU/LV + oxaliplatin, nal-IRI + 5-FU/LV, or nab-paclitaxel + gemcitabine. The randomization will be stratified based on region (East Asia vs. rest of the world) and ECOG performance status (0 vs 1). Patients randomized to nal-IRI + 5 FU/LV will undergo serial ECG recordings and time-matched pharmacokinetic sampling to assess any relationship between blood levels of nal-IRI and possible changes in QTc intervals.	*Deleted text*

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		During Part 2, a regular review of safety data will be conducted by an independent Data and Safety Monitoring Board (DSMB). The DSMB will consist of oncology and statistical experts, independent of the Sponsor. The timing of the safety reviews, and the workings of the DSMB, will be detailed in the DSMB charter. The DSMB is a precaution in the event of unanticipated toxicities, and the study will not be stopped early on the basis of differences in efficacy, therefore no prospective adjustment of the final significance levels is planned on the basis of this review.	
14, 34	Synopsis, 3.1	Translational Research: Translational research components will include collection of blood samples (Parts 1 and 2) and archived tumor (during screening, if available) to look for potential biomarkers. Analyses will include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), or enzyme levels (e.g. MMP9).	Translational Research: Translational research components will include collection of blood samples and archived tumor (during screening, if available) to look for potential biomarkers. Analyses **may** include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), or enzyme levels (e.g. MMP9).
35	3.2.1	Considering these expected toxicities, Arm 1 will be evaluated for safety and tolerability in Part 1 of the study as described below.	*Deleted text*
13, 35	Synopsis, 3.2	3.2.2 DLT Definition for Part 1 (Nal-IRI + 5-FU/LV + Oxaliplatin) As part of this study, pharmacogenomic data will be collected on all patients for determination of UGT1A1*28 status.	3.2.2 DLT Definition (Nal-IRI + 5-FU/LV + Oxaliplatin) (*Deleted text)*
35	3.2	3.2.3 Part 2 Dose Confirmation (Arm 1) The purpose of Part 1 is to determine which dose levels of oxaliplatin and nal-IRI are compatible when nal-IRI is used instead of conventional irinotecan, as described in Section 3.1.	(*Deleted text)*

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		Final determination of the Part 2 dose for Arm 1 will be made after all patients in the Part 1A (dose escalation) and Part 1B (expansion cohort) have completed two scheduled assessments (approximately 16 weeks of therapy; unless withdrawn at an earlier time point due to disease progression or drug-related toxicity) and will take into account all available data from the expansion cohort and also all available updated data for patients still receiving ongoing therapy in the other dose level cohorts. Data will include DLT, SAE, and grade 3-4 adverse events along with any available pharmacokinetic, pharmacogenomic, pharmacodynamic results and any initial efficacy data.	
14, 36	Synopsis, 4	Approximately 54 patients will be enrolled in Part 1. An additional 150 patients (50 patients per arm) will be enrolled during Part 2. Therefore, the total enrollment for the study will be approximately 204 patients.	Approximately 54 patients will be enrolled in the study.
36	4	4.1 Method of Assigning Patients to Treatment Groups 4.1.1 Part 1 It is expected that multiple sites will participate in Part 1 of this trial. Enrollment will be based on the availability of patients at each site and the availability of slots in each cohort. Slots must be confirmed by the Sponsor, or designee, prior to consenting patients to Part 1. 4.1.2 Part 2 Three arms are planned to enroll in parallel in Part 2, and enrollment into Part 2 will begin once the dose has been confirmed for Arm 1 (see Section 3.2.3). After all screening assessments have been completed, patients will be randomized 1:1:1 using a computerized interactive web response system (IWRS). Randomization must occur within	It is expected that multiple sites will participate in this trial. Enrollment will be based on the availability of patients at each site and the availability of slots in each cohort. Slots must be confirmed by the Sponsor, or designee, prior to consenting patients to **the study**.

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		7 days of planned dosing. The randomization will be stratified based on region (East Asia vs. rest of the world).	
37	4.1	Protocol Version 5.0 Update: The original plan in the study was to evaluate dose levels in Part 1 as described in the table above. Dose level cohorts 1, -1 and -2B have been evaluated. Dose levels 1 and -2B were considered to be not tolerable. Dose level -1 (oxaliplatin 60 mg/m^2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable. Following the completion of the three predefined dose level cohorts, this protocol amendment introduces a new dose level -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) for evaluation Dose levels 2 and -2A will not be evaluated in the study.	The original plan in the study was to evaluate dose levels as described in the table above. Dose level cohorts 1, -1 and -2B have been evaluated. Dose levels 1 and -2B were considered to be not tolerable. Dose level 1 (oxaliplatin 60 mg/m2 + nal-IRI 60 mg/m^2) was determined to be safe and tolerable. Following the completion of the three predefined dose level cohorts, a new dose level -3 (oxaliplatin 70 mg/m^2 + nal-IRI 65 mg/m^2) was introduced following a protocol amendment (protocol Version 5.0) **to evaluate its safety and tolerability**. Dose levels 2 and -2A **were considered not to** be evaluated in the study. **Prior to this Version 5.0, the enrollment of dose level cohorts 1, -1 and -2B has been completed.**
14, 38-39	Synopsis, 5.1	Inclusion Criteria for All Parts of Study: a) Histologically or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting: • Part 1: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to enrollment • Part 2: must have metastatic disease diagnosed within 6 weeks prior to randomization; unresectable or locally advanced disease is **not** allowed c) ECOG performance status of 0 or 1 at both Screening and within 72 hours prior to enrollment/randomization. Two observers will be required to assess ECOG. If different, the lowest assessment will be used for the eligibility evaluation at each assessment g) ECG without any clinically significant findings	Inclusion Criteria: a) Histologically or cytologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to **Screening** c) ECOG performance status of 0 or 1 at Screening, and within 72 hours prior to **first dose if first dose occurs more than 72 hours post screening**. Two observers will be required to assess ECOG. If different, the lowest assessment will be used for the eligibility evaluation at each assessment **(criterion applicable only for Part 1A)** g) ECG without any clinically significant findings **(e.g. QTc ≤450 ms for males and ≤470 ms for females and no known arrhythmias)**

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			l) Patient has a Karnofsky performance status (KPS) ≥ 70 at Screening, and within 72 hours prior to date of first dose if first dose occurs more than 72 hours after screening. Two observers will be required to assess KPS. If discrepant, the one with the lowest assessment will be considered true (criterion applicable only for Part 1B, added in protocol Version 6.0)
15-16, 39-40	Synopsis,5.2	Exclusion criteria a) Prior treatment of pancreatic cancer in the metastatic setting (or locally advanced setting, Part 1 only) with surgery, radiotherapy, chemotherapy or investigational therapy (Note: placement of biliary stent is allowed) b) Prior treatment of pancreatic cancer with cytotoxic doses of systemic anti-tumor therapy (Note: patients receiving prior treatment with chemotherapy as a radiation sensitizer are eligible if ≥ 6 months has elapsed from completion of therapy) c) Uncontrolled CNS metastases (patients who require steroids should be on a stable or decreasing dose) g) Known hypersensitivity to any of the components of nab-paclitaxel or gemcitabine (Part 2 only) j) Use of strong CYP3A4 inhibitors or inducers, or presence of any other contraindications for irinotecan[1] k) Presence of any contraindications for 5-FU, leucovorin, oxaliplatin, gemcitabine, or nab-paclitaxel.	Exclusion criteria a) Prior treatment of pancreatic cancer in the metastatic setting (or locally advanced setting) with surgery, radiotherapy, chemotherapy or investigational therapy (Note: **palliative radiotherapy is permitted;** placement of biliary stent is allowed) b) 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 (modified in protocol Version 6.0)** c) Uncontrolled CNS metastases (**Note:** patients who require steroids should be on a stable or decreasing dose **to be eligible**) g) **Exclusion Criteria removed (protocol Version 6.0)** j) Use of strong CYP3A4 inhibitors or inducers**, or strong UGT1A1 inhibitors (patients are ineligible if unable to discontinue the use of strong CYP3A4 or UGT1A1 inhibitors at least 1 week or strong CYP3A4 inducers at least 2 weeks prior to receiving first dose of irinotecan liposome injection)**, or presence of any other contraindications for irinotecan[1]

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			k) Presence of any contraindications for **nal-IRI**, 5-FU, leucovorin, or oxaliplatin. l) **Exclusion Criteria removed (protocol Version 6.0)**
		l) Use of strong CYP2C8 inhibitors or inducers, or presence of any other contraindications for nab-paclitaxel or gemcitabine (Part 2 only)[2] n) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 6 months following the last dose of study drug.[3] p) Documented serum albumin <3 g/dL at Screening Visit and within 72 hours prior to enrollment/randomization (both labs at screening and prior to enrollment/randomization may be confirmed locally) [1] See Section 6.8 for examples of strong CYP3A4 inhibitors or inducers. [2] See Section 6.8 for examples of strong CYP2C8 inhibitors or inducers. [3] For a description of highly effective contraceptive measures, please see Appendix 1.	n) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy **within 7 days prior to the first dose** based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 6 months following the last dose of study drug.[2] p) Documented serum albumin <3 g/dL at Screening, and within 72 hours prior to **first dose if first dose occurs more than 72 hours post screening** (both labs at screening and prior to **first dose** may be confirmed locally) **r) Previous treatment with irinotecan-based, nab-paclitaxel-based or gemcitabine-based resulting in disease progression (added in protocol Version 6.0)** [1] See Section 6.8 for examples of strong CYP3A4 **or UGT1A1** inhibitors or **CYP3A4** inducers. [2] For a description of highly effective contraceptive measures, please see Appendix 1.
40	5.3.1	• A study drug related adverse event, prior to disease progression, which: ○ … ○ would result in a third dose reduction in any single study drug (in a patient having already experienced 2 previous dose reductions)	• A study drug related adverse event, prior to disease progression, which: ○ … ○ would result in a **fourth** dose reduction in any single study drug (in a patient having already experienced **3** previous dose reductions)

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		○ requires discontinuation of nal-IRI (Arm 1 only)	○ requires discontinuation of nal-IRI
40	5.3.1	A patient who discontinues study medication has **not** withdrawn from the study and must continue with all ongoing protocol requirements, as detailed in Section 5.3.3.	A patient who discontinues study medication **and** has **not** withdrawn from the study must continue with all ongoing protocol requirements, as detailed in Section 5.3.3.
41	5.3.3	At the time of withdrawal from the study, it should be clarified with the patient whether they still consent to be followed up for survival status only (including where appropriate through publicly available records) and any such consent to ongoing survival follow up must be documented in both the source hospital records and the eCRF.	At the time of **discontinuation** from the study **treatment**, it should be clarified with the patient whether they still consent to be followed up for survival status only (including where appropriate through publicly available records) and any such consent to ongoing survival follow up must be documented in both the source hospital records and the eCRF.
41	6.1.1.1	Nal-IRI must be diluted prior to administration. The diluted solution is physically and chemically stable for 4 hours at room temperature (15 – 25 °C), but it is preferred to be stored at refrigerated temperatures (2 – 8 °C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2 – 8 °C), and within 4 hours if kept at room temperature (15 – 25 °C).	Nal-IRI must be diluted prior to administration. The diluted solution is physically and chemically stable for 4 hours at room temperature (15 – 25 °C), but it is preferred to be stored at refrigerated temperatures (2 – 8 °C). The diluted solution must not be frozen, **and must be protected from light until infusion**. Because of possible microbial contamination during dilution, the diluted solution **should be administered** within 24 hours **of preparation** if refrigerated (2 – 8 °C), and within 4 hours if kept at room temperature (15 – 25 °C).
42-43	6.1.1.4	**Neutropenia** Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan and nal-IRI. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia at the investigator's discretion, provided it is administered within parameters specified in Section 6.7.2.	**Neutropenia** Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan and nal-IRI. **In patients with metastatic pancreatic cancer in the NAPOLI-1 study receiving irinotecan liposome injection/5-FU/LV, the incidence of grade 3 or 4 neutropenia was higher among Asian patients (18 of 33 [55%]) compared to White patients (13 of 73 [18%]).** Neutropenic complications should be managed promptly with antibiotic support. **Granulocyte-colony stimulating**

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			factor (G-CSF) may be used to manage neutropenia at the investigator's discretion**. Prophylactic use of G-CSF will be permitted if patients are considered high risk in the opinion of the investigator as** specified in Section **6.7.1**.
44	6.2	Depending on the assigned treatment arm, patients may be treated with one or more of the following approved therapies: • 5-FU/LV • oxaliplatin • nab-paclitaxel • gemcitabine	**Patients will** be treated with one or more of the following approved therapies: • 5-FU/LV • oxaliplatin
44	6.2.2	Refer to the country specific package inserts or SmPC for details on storage and handling for 5-FU and leucovorin, oxaliplatin, nab-paclitaxel, and gemcitabine.	Refer to the country specific package inserts or SmPC for details on storage and handling for 5-FU and leucovorin **and** oxaliplatin.
44	6.2.3	Sites participating in this protocol will source their own combination therapy supplies. However, for sites where this is not possible due to country legal or regulatory restrictions, Ipsen will provide commercially available 5-FU and leucovorin, oxaliplatin, nab-paclitaxel and gemcitabine as required by their enrolled patients for their specific treatment regimen. Ipsen sourced combination therapy supplies will be labeled in accordance with local regulatory requirements, and site accountability for all Ipsen sourced clinical trial material is required.	Sites participating in this protocol will source their own combination therapy supplies. However, for sites where this is not possible due to country legal or regulatory restrictions, Ipsen will provide commercially available 5-FU, leucovorin **and** oxaliplatin as required by their enrolled patients for their specific treatment regimen. Ipsen sourced combination therapy supplies will be labeled in accordance with local regulatory requirements, and site accountability for all Ipsen sourced clinical trial material is required **and will be monitored by the sponsor or its representatives**.
44-45	6.2.4	6.2.4.3 Potential Toxicities with Nab-paclitaxel and Gemcitabine (Part 2 Arm 3) The most common adverse reactions (≥20%) for single agent gemcitabine are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema.	*Deleted text*

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		The following adverse events are relatively common (≥ 20%) with nab-paclitaxel and gemcitabine combination treatment and are to be expected with the addition of nal-IRI: neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. Severe hypersensitivity reactions with fatal outcome have been reported with nab-paclitaxel treatment; see Section 6.4 for guidelines on the management of infusion reactions. Additional adverse events may be anticipated, as described in the package inserts for nab-paclitaxel and gemcitabine [13] [14].	
45	6.3.1	In Part 1, Patients will receive the oxaliplatin infusion 2 hours after the completion of the nal-IRI infusion and will receive leucovorin 30 min after oxaliplatin. If no infusion reactions are seen, Part 2 patients can receive oxaliplatin directly after completion of the nal-IRI infusion and leucovorin directly after completion of oxaliplatin. If any grade 3 or higher infusion reactions are seen in Part 2 patients, the DSMB may elect to revert back to the original observation periods.	Patients will receive the oxaliplatin infusion 2 hours after the completion of the nal-IRI infusion and will receive leucovorin 30 min after oxaliplatin.
45	6.3	6.3.2 Part 2 Arm 2: Nal-IRI + 5-FU/LV The order of the infusions to be administered in the clinic will be as follows: nal-IRI will be administered first, followed by LV, followed by 5-FU. 6.3.2.1 Part 2 Arm 2 Premedication All patients must be premedicated prior to nal-IRI infusion and 5-FU/LV infusion with standard doses of dexamethasone and a 5-HT3 antagonist, or equivalent other anti-emetics according to standard institutional practices for irinotecan and 5-FU administration, or the SmPC for sites	*Deleted text*

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		located in the EU. In situations where differences in standard institutional practices and recommendations within the country relevant SmPC occur, standard institutional practice will take precedence. Atropine may be prescribed prophylactically, according to standard institutional practices, for patients who experienced acute cholinergic symptoms in the previous cycles.	
45	6.3	6.3.3 Doses and Administration of Nal-IRI (Part 1 and Part 2 Arms 1 and 2) Nal-IRI will be administered as follows: Part 1: Nal-IRI will be administered at doses of 60 mg/m^2 to 80 mg/m^2 (as outlined in Section 4.2). Part 2: 1. ARM 1 - dose of nal-IRI will be selected at the end of Part 1 2. ARM 2 - 80mg/m^2	**6.3.2 Doses and Administration of Nal-IRI** Nal-IRI will be administered at doses of 60 mg/m^2 to 80 mg/m^2 (as outlined in Section 4.**1**).
45-46	6.3	6.3.4 Doses and Administration of 5-FU and Leucovorin (Part 1 and Part 2 Arms 1 and 2) Leucovorin should be administered prior to the 5-FU infusion (in Part 1, leucovorin will not be given concurrently with oxaliplatin, see Section 6.3.1).	6.3.**3** Doses and Administration of 5-FU and Leucovorin Leucovorin should be administered prior to the 5-FU infusion.
46	6.3	6.3.5 Doses and Administration of Oxaliplatin (Part 1 and Part 2 Arm 1 only) • In Part 1, oxaliplatin will be administered at varying dose levels as indicated in Table 6 (from 60 mg/m^2 - 85 mg/m^2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle • In Part 2 Arm 1, oxaliplatin will be administered at a dose to be identified in Part 1 (as outlined in Section 4.2) IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle	6.3.**4** Doses and Administration of Oxaliplatin • Oxaliplatin will be administered at varying dose levels as indicated in Table 5 (from 60 mg/m2 - 85 mg/m2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle
46	6.3	6.3.6 Part 2 Arm 3: Nab-paclitaxel + Gemcitabine	*Deleted text*

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		The order of the infusions to be administered in the clinic will be as follows: nab-paclitaxel will be administered first, followed by gemcitabine. 6.3.6.1 Part 2 Arm 3 Premedication All patients receiving nab-paclitaxel and gemcitabine should be pre-medicated per the respective package inserts. If different institutional guidelines exist for premedication of weekly nab-Paclitaxel and/or gemcitabine, the investigator should use their standard practice or the SmPC for sites located in the EU. 6.3.7 Doses and Administration of Nab-paclitaxel and Gemcitabine (Part 2 Arm 3) • Nab-paclitaxel will be administered at 125 mg/m^2 IV over 35 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle • Gemcitabine will be administered at 1000 mg/m^2 IV over 30 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle	
46	6.4	The guidelines described in this section can be followed in case of infusion reactions to any study treatment given per protocol (e.g. nal-IRI, oxaliplatin, nab-paclitaxel, etc.).	The guidelines described in this section can be followed in case of infusion reactions to any study treatment given per protocol (e.g. nal-IRI, oxaliplatin).

<table>
<tr>
<td>47-50</td>
<td>6.5</td>
<td>
6.5 Dose Modifications (Part 1 and Part 2)
If oxaliplatin is not well tolerated in patients enrolled in Arm 1, oxaliplatin may be discontinued and patients may continue to receive nal-IRI + 5-FU/LV at the discretion of the Investigator.
Any patient who has 2 dose reductions and experiences an adverse event that would require a third dose reduction must be discontinued from study treatment.

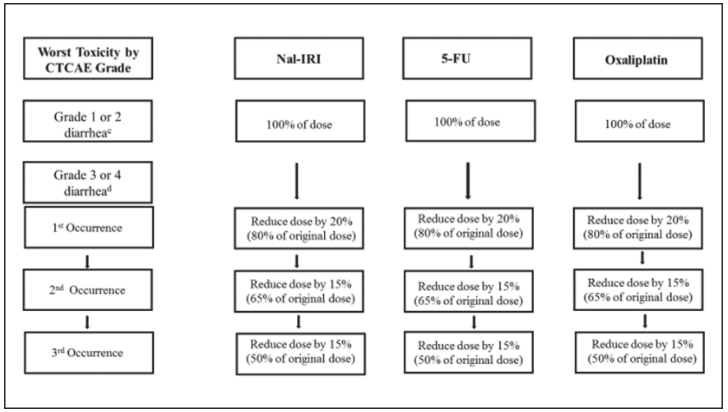
For all tables below, patient should be withdrawn from study treatment if more than 2 dose reductions are required.

Table 7: Part 1 and Part 2 Arm 1 (nal-IRI + 5-FU/LV + oxaliplatin) Dose Modifications for Hematologic Toxicities
<table>
<tr><th>Worst Toxicity by CTCAE Grade</th><th>Nal-IRI</th><th>5-FU</th><th>Oxaliplatin</th></tr>
<tr><td>Grade 2 hematotoxicity</td><td colspan="3">100% of previous dose</td></tr>
<tr><td>Grade 3- 4 neutropenia (ANC ≤ 1000/mm^3) or febrile neutropenia and/or thrombocytopenia[a]</td><td colspan="3">1st occurrence: Reduce dose by 25%
2nd occurrence: Reduce dose another 25% (50% of original dose)</td></tr>
<tr><td>Other Grade 3 or 4 hematologic toxicities not specifically listed above</td><td colspan="3">1st occurrence: Reduce dose by 25%
2nd occurrence: Reduce dose another 25% (50% of original dose)</td></tr>
</table>
[a] Consider the use of G-CSF for patients who experience ≥ Grade 3 neutropenia or febrile neutropenia (see Section 6.7.2 for details).
</td>
<td>
6.5 Dose Modifications
If oxaliplatin is not well tolerated, oxaliplatin may be discontinued and patients may continue to receive nal-IRI + 5-FU/LV at the discretion of the Investigator.

Any patient who has 3 dose reductions and experiences an adverse event that would require a fourth dose reduction must be discontinued from study treatment.

For all tables below, patient should be withdrawn from study treatment if more than 3 dose reductions are required.

Table 6: Dose Modifications for Hematologic Toxicities[(a,b,c,d)]
<table>
<tr><th>Worst Toxicity by CTCAE Grade</th><th>Nal-IRI</th><th>5-FU</th><th>Oxaliplatin</th></tr>
<tr><td>Grade 2 hematotoxicity</td><td colspan="3">100% of previous dose</td></tr>
<tr><td>Grade 3- 4 neutropenia[e] (ANC ≤ 1000/mm^3) or febrile neutropenia and/or thrombocytopenia</td><td colspan="3">1st occurrence: Reduce dose by 20% (80% of original dose)
2nd occurrence: Reduce dose by another 15% (65% of original dose)
3rd occurrence: Reduce dose by another 15% (50% of original dose)</td></tr>
<tr><td>Other Grade 3 or 4 hematologic toxicities not specifically listed above</td><td colspan="3">1st occurrence: Reduce dose by 20% (80% of original dose)
2nd occurrence: Reduce dose by another 15% (65% of original dose)
3rd occurrence: Reduce dose by another 15% (50% of original dose)</td></tr>
</table>
Any toxicity ≥ Grade 2 can justify a dose reduction if medically indicated following above guidance
[b] 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.
[c] Patients who require more than 3 dose reductions must discontinue study treatment.
[d] Prophylactic use of Granulocyte-colony stimulating factor (G-CSF) will be permitted if patients are considered high risk in the opinion of the investigator
</td>
</tr>
</table>

<table>
<tr><th colspan="2">Version Date</th><th>29 SEPTEMBER 2017 (VERSION 5.0)</th><th>11 APRIL 2018 (VERSION 6.0)</th></tr>
<tr><th>Page</th><th>Section</th><th>WAS</th><th>IS</th></tr>
<tr><td></td><td></td><td></td><td>[e] Consider the use of G-CSF for patients who experience ≥ Grade 3 neutropenia or febrile neutropenia</td></tr>
<tr><td></td><td></td><td></td><td>New table added:
Table 7: Dose Modifications for Diarrhea[a,b]
 

[a] Any toxicity ≥ Grade 2 can justify a dose reduction if medically indicated following above guidance
[b] Patients who require more than 3 dose reductions must discontinue study treatment
[c] Grade 1 diarrhea: 2-3 stools/day > pretreatment; Grade 2 diarrhea: 4-6 stools/day > pretreatment
[d] Grade 3 diarrhea: 7-9 stools/day > pretreatment; Grade 4 diarrhea: life threatening consequences
[e] Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms (acute diarrhea. and abdominal cramps during or within 24 hours after nal-IRI administration)</td></tr>
</table>

Table 8: Part 1 and Part 2 Arm 1 (nal-IRI + 5-FU/LV + oxaliplatin) Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[a,d,e]

Worst Toxicity by CTCAE Grade	Nal-IRI	5-FU	Oxaliplatin
Grade 1 or 2, including diarrhea[b]	100% of previous dose	100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity	100% of previous dose, except for Grade 2 sensory neuropathy
Grade 3 or 4, including diarrhea[c] (except nausea and vomiting)	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose) **Note:** except for Grade 3 or 4 hand foot syndrome	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose by another 25% (50% of original dose)
Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy AND 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose by another 25% (50% of original dose)		
Grade 2 hand foot syndrome	100% of previous dose[d]	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)	100% of previous dose[d]

Table 8: Dose Modifications for Non-Hematological Toxicities Other than Diarrhea, Asthenia and Grade 3 Anorexia[a,b,e]

Worst Toxicity by CTCAE Grade	Nal-IRI	5-FU	Oxaliplatin
Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy	Optimize anti-emetic therapy AND 1st occurrence: Reduce dose by 20% (80% of original dose) 2nd occurrence: Reduce dose by another 15% (65% of original dose) 3rd occurrence: Reduce dose by another 15% (50% of original dose)		
Grade 2 hand foot syndrome	100% of previous dose[b]	1st occurrence: Reduce dose by 20% (80% of original dose) 2nd occurrence: Reduce dose by another 15% (65% of original dose) 3rd occurrence: Reduce dose by another 15% (50% of original dose)	100% of previous dose[b]
Grade 3 or 4 hand foot syndrome	100% of previous dose[b]	Discontinue therapy	100% of previous dose[b]
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	100% of previous dose[b]	Discontinue therapy	100% of previous dose[b]
Sensory neuropathy	100% of previous dose[b]	100% of previous dose[b]	Grade 2, persistent: Reduce dose by 20% (80% of original dose) Grade 3, recovers prior

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		Grade 3 or 4 hand foot syndrome	100% of previous dose[d]	Discontinue therapy	100% of previous dose[d]				to next cycle: Reduce dose by 35% (65% of original dose) Grade 3, recurrent: Reduce dose by 15%[d] (50% of original dose) Grade 3, persistent or Grade 4: Discontinue therapy[c]
		Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	100% of previous dose[d]	Discontinue therapy	100% of previous dose[d]				
		Sensory neuropathy	100% of previous dose[d]	100% of previous dose[d]	Grade 2, persistent: Reduce dose by 25% Grade 3, recovers prior to next cycle: Reduce dose by 25% Grade 3, persistent: Discontinue therapy[f] Grade 4: Discontinue therapy[f]				
		[a] Asthenia and Grade 3 Anorexia do not require dose modification [b] Grade 1 diarrhea: 2-3 stools/day > pretreatment; Grade 2 diarrhea: 4-6 stools/day > pretreatment [c] Grade 3 diarrhea: 7-9 stools/day > pretreatment; Grade 4 diarrhea: > 10 stools/day > pretreatment. See Section 6.7.2 for therapy of diarrhea. [d] Any toxicity ≥ Grade 2, except asthenia and alopecia, can justify a dose reduction if medically indicated [e] Patients who require more than 2 dose reductions must be withdrawn from the study [f] Patients who discontinue therapy due to oxaliplatin-related neuropathy may remain on study and continue to receive nal-IRI + 5-FU/LV				[a] Asthenia and Grade 3 Anorexia do not require dose modification [b] Any toxicity ≥ Grade 2, except asthenia and alopecia, can justify a dose reduction if medically indicated [c] Patients who discontinue therapy due to oxaliplatin-related neuropathy may remain on study and continue to receive nal-IRI + 5-FU/LV [d] At the discretion of the investigator, patients can discontinue oxaliplatin therapy if Grade 3 persistent sensory neuropathy occurs. [e] Patients who require more than 3 dose reductions must discontinue study treatment			
						Grade 3 or 4 hepatic, renal, respiratory or other toxicities	1st occurrence: Reduce dose by 20% (80% of original dose) 2nd occurrence: Reduce dose by another 15% (65% of original dose) 3rd occurrence: Reduce dose by another 15% (50% of original dose)		

Table 9: Part 2 Arm 2 (nal-IRI + 5-FU/LV) Dose Modifications for Hematologic Toxicities

Worst Toxicity by CTCAE Grade	Nal-IRI	5-FU
Grade 2 neutropenia (ANC <1500 - 1000 cells/mm^3)	100% of previous dose	
Grade 3 or 4 neutropenia (ANC ≤ 1000/mm^3) or febrile neutropenia[a]	1st occurrence: Reduce dose to 60 mg/m^2 2nd occurrence: Reduce dose to 50 mg/m^2	1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)
≥ Grade 2 thrombocytopenia (Grade 2: platelets ≤ 75,000/mm^3 – 50,000/mm^3 OR Grade 3-4: platelets < 50,000/mm^3)	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 60 mg/m^2 2nd occurrence: Reduce dose to 50 mg/m^2	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)
Other hematologic toxicities not specifically listed above	<u>If Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose to 60 mg/m^2 2nd occurrence: Reduce dose to 50 mg/m^2	<u>If ≤ Grade 2:</u> 100% of previous dose <u>If ≥ Grade 3:</u> 1st occurrence: Reduce dose by 25% 2nd occurrence: Reduce dose another 25% (50% of original dose)

[a] Consider the use of G-CSF for patients who experience ≥ Grade 3 neutropenia or febrile neutropenia (see Section 6.7.2 for details).

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<tr><td></td><td></td><td>Table 10: Part 2 Arm 2 (nal-IRI + 5-FU/LV) Dose Modifications for Non-Hematological Toxicities Other than Asthenia and Grade 3 Anorexia[a,d,e]
<table>
<tr><th>Worst Toxicity by CTCAE Grade</th><th>Nal-IRI</th><th>5-FU</th></tr>
<tr><td>Grade 1 or 2, including diarrhea[b]</td><td>100% of previous dose</td><td>100% of previous dose, except for Grade 2 hand foot syndrome, Grade 2 cardiac toxicity, or any grade neurocerebellar toxicity</td></tr>
<tr><td>Grade 3 or 4, including diarrhea[c] (except nausea and vomiting)</td><td>1st occurrence: Reduce dose to 60 mg/m^2
2nd occurrence: Reduce dose to 50 mg/m^2</td><td>1st occurrence: Reduce dose by 25%
2nd occurrence: Reduce dose another 25% (50% of original dose)
Note: except for Grade 3 or 4 hand foot syndrome</td></tr>
<tr><td>Grade 3 or 4 nausea and/or vomiting despite anti-emetic therapy</td><td>Optimize anti-emetic therapy AND reduce dose to 60 mg/m^2 ; if the patient is already receiving 60 mg/m^2, reduce dose to 50 mg/m^2</td><td>Optimize anti-emetic therapy AND reduce dose by 25%; if the patient is already receiving a reduced dose, reduce dose an additional 25%</td></tr>
<tr><td>Grade 2 hand foot syndrome</td><td>100% of previous dose[d]</td><td>1st occurrence: Reduce dose by 25%
2nd occurrence: Reduce dose another 25% (50% of original dose)</td></tr>
<tr><td>Grade 3 or 4 hand foot syndrome</td><td>100% of previous dose[d]</td><td>Discontinue therapy</td></tr>
</table></td><td>Deleted table</td></tr>
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		Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity | 100% of previous dose[d] | Discontinue therapy [a] Aesthenia and Grade 3 Anorexia do not require dose modification [b] Grade 1 diarrhea: 2-3 stools/day > pretreatment; Grade 2 diarrhea: 4-6 stools/day > pretreatment [c] Grade 3 diarrhea: 7-9 stools/day > pretreatment; Grade 4 diarrhea: > 10 stools/day > pretreatment [d] Any toxicity ≥ Grade 2, except anemia and alopecia, can justify a dose reduction if medically indicated [e] Patients who require more than 2 dose reductions must be withdrawn from the study	
50-51	6.5	6.5.2 Nal-IRI Dose Modifications for UGT1A1*28 Positive Patients (Arms 1 and 2) The protocol does not contain formal recommendations on nal-IRI dose modifications as a consequence of homozygosity. All patients should receive the full starting dose of nal-IRI. All Arm 1 patients should start at the dose level identified from Part 1, while all Arm 2 patients will begin dosing at 80 mg/m^2.	6.5.**1** Nal-IRI Dose Modifications for UGT1A1*28 Positive Patients The protocol does not contain formal recommendations on nal-IRI dose modifications as a consequence of homozygosity. All patients should receive the full starting dose of nal-IRI.
51	6.5	6.5.3 Arm 3 Dose Modifications Dose level reductions required due to toxicity related to nab-paclitaxel and gemcitabine should be made following the guidelines outlined in Table 11.	*Deleted section*

Table 11: Dose Level Reductions for Nab-paclitaxel and Gemcitabine

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reductions required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia are provided in Table 12 and adjustments related to other toxicities are provided in Table 13.

Table 12: 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 doses
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 doses
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 doses

ANC = absolute neutrophil count

Table 13: Nab-paclitaxel and Gemcitabine Dose Modifications for Other Adverse Drug Reactions

Adverse Drug Reaction	Nab-paclitaxel	Gemcitabine

<table>
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<tr><th>Page</th><th>Section</th><th colspan="2">WAS</th><th>IS</th></tr>
<tr><td></td><td></td><td colspan="2"><table>
<tr><td>Febrile Neutropenia:
Grade 3 or 4</td><td colspan="2">Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level</td></tr>
<tr><td>Peripheral Neuropathy:
Grade 3 or 4</td><td>Withhold until improves ≤ Grade 1; resume at next dose level</td><td>No dose reduction</td></tr>
<tr><td>Cutaneous Toxicity:
Grade 2 or 3</td><td colspan="2">Reduce to next lower dose level; discontinue treatment if toxicity persists</td></tr>
<tr><td>Gastrointestinal Toxicity:
Grade 3 mucositis or diarrhea</td><td colspan="2">Withhold until improves to ≤ Grade 1; resume at next dose level</td></tr>
</table></td><td></td></tr>
<tr><td>51</td><td>6.5</td><td colspan="2">6.5.<u>4</u> Other Toxicities Requiring Special Attention
<u>For all treatment arms,</u> QTc prolongation that occurs in the setting of diarrhea induced electrolyte imbalance should be treated with appropriate electrolyte repletion.</td><td>6.5.2 Other Toxicities Requiring Special Attention
QTc prolongation that occurs in the setting of diarrhea induced electrolyte imbalance should be treated with appropriate electrolyte repletion.</td></tr>
</table>

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51	6.5	6.5.5 Rules for Dose Omissions and Modified Schedules The following guidance should be followed when all study drugs in any arm are held/missed: For both Part 1 and Part 2, the maximum delay between the date of a scheduled but missed dose and the planned next dose should be up to 14 days. In Part 2, Arm 3, • If **Day 1** doses are held/missed: the doses intended for Day 1 of a cycle should be delayed, such that the start of that cycle will not begin until the doses are actually administered to the patient • If **Day 8** doses are held/missed: the cycle will continue per protocol and those doses will be considered missed. • If **Day 15** doses are held/missed: the dose will be considered missed and dosing will continue with Day 1 of the next cycle when toxicity recovers.	6.5.**3** Rules for Dose Omissions and Modified Schedules The following guidance should be followed when all study drugs are held/missed: The maximum delay between the date of a scheduled but missed dose and the planned next dose should be up to 14 days.
51	6.6	• Date and quantity of study drug administered to each patient	• Date and quantity of study drug administered to each patient **(the start and stop date/time of infusion of drug should be recorded for each patient at each dose)**
52	6.6	At the conclusion of the study, the monitor will package and ship all unused vials of study drug back to Sponsor for destruction.	At the conclusion of the study, the monitor will **perform accountability on** all unused vials of study drug. **Once accountability is complete**, destruction **may be performed at the site, or if the site does not have a destruction process, the monitor may ship the supplies back to the sponsor. In case of destruction at the site, the method should be documented in the site files.**

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52	6.7	6.7.1 Antiemetic Medications Dexamethasone and a 5-HT3 blocker (e.g., ondansetron or granisetron) will be administered as premedications to all patients assigned to Arm 1 and Arm 2 unless contraindicated for the individual patient. For patients randomized to Arm 2, during cycle 1 ECG monitoring, consider alternatives to 5-HT3 blockers which have been associated with QT changes. Antiemetics will also be prescribed as clinically indicated during the study period.	*Deleted section*
52	6.7	6.7.2 Granulocyte Colony Stimulating Factors Use of granulocyte colony-stimulating factors (G-CSF) is permitted to treat patients with neutropenia or neutropenic fever. In Part 1, prophylactic use of G-CSF will be permitted only in those patients who have had at least one episode of grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy. In Part 2, prophylactic use of G-CSF is recommended for patients who have had at least one episode of grade 3 or 4 neutropenia or neutropenic fever while receiving study therapy, however primary prophylaxis with G-CSF may be considered for high risk patients, according to local institutional polices and/or established guidelines [32] [33] [34].	6.7.**1** Granulocyte Colony Stimulating Factors **Deaths due to sepsis following severe** neutropenia **have been reported in patients treated with irinotecan and nal-IRI. In patients with metastatic pancreatic cancer in the NAPOLI-1 study receiving irinotecan liposome injection/5-FU/LV, the incidence of** grade 3 or 4 neutropenia **was higher among Asian patients [18 of 33 (55%)] compared to White patients [13 of 73 (18%)]. Neutropenic complications should be managed promptly with antibiotic support. G-CSF may be used to manage neutropenia at the investigator's discretion. Prophylactic use of G-CSF will be permitted if patients are considered high risk in the opinion of the investigator [33] [34] [35].**

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<tr><td>53</td><td>6.7.2</td><td>Table 14: Recommendations for Management of Chemotherapy Induced Diarrhea
<table>
<tr><th>Clinical Presentation</th><th>Intervention</th></tr>
<tr><td>Diarrhea, any grade</td><td>Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea; 2 mg every 4 hours for 5-FU induced diarrhea): continue until diarrhea-free for ≥ 12 hours</td></tr>
<tr><td>Diarrhea persists on loperamide for > 24 hours</td><td>Oral fluoroquinolone x 7 days</td></tr>
<tr><td>Diarrhea persists on loperamide for > 48 hours</td><td>Stop loperamide; hospitalize patient; administer IV fluids</td></tr>
<tr><td>ANC < 500 cells/μL, regardless of fever or diarrhea</td><td>Oral fluoroquinolone (continue until resolution of neutropenia)</td></tr>
<tr><td>Fever with persistent diarrhea, even in the absence of neutropenia</td><td>Oral fluoroquinolone (continue until resolution of fever and diarrhea)</td></tr>
</table></td><td>Table 9: Recommendations for Management of Chemotherapy Induced Diarrhea
<table>
<tr><th>Clinical Presentation</th><th>Intervention</th></tr>
<tr><td>Diarrhea, any grade</td><td>Oral loperamide (2 mg every 2 hours for irinotecan induced diarrhea; 2 mg every 4 hours for 5-FU induced diarrhea): continue until diarrhea-free for ≥ 12 hours
Oral electrolyte replacement</td></tr>
<tr><td>Diarrhea persists on loperamide for > 24 hours</td><td>Oral fluoroquinolone x 7 days</td></tr>
<tr><td>Diarrhea persists on loperamide for > 48 hours</td><td>Stop loperamide; hospitalize patient; administer IV fluids</td></tr>
<tr><td>ANC < 500 cells/μL, regardless of fever or diarrhea</td><td>Oral fluoroquinolone (continue until resolution of neutropenia)</td></tr>
<tr><td>Fever with persistent diarrhea, even in the absence of neutropenia</td><td>Oral fluoroquinolone (continue until resolution of fever and diarrhea)</td></tr>
</table></td></tr>
<tr><td>53</td><td>6.8</td><td>The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan: St. John’s Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), ketoconazole, itraconazole, troleandomycin, erythromycin, diltiazem and verapamil.

Treatment with these agents and any others that interact with irinotecan, 5-FU, oxaliplatin, or gemcitabine should be avoided wherever possible. Additionally, nab-paclitaxel is catalyzed by CYP2C8 and CYP3A, therefore Part 2 patients randomized to Arm 3 should avoid concomitant treatment with strong inhibitors (ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir and nelfinavir) or inducers (rifampicin, carbamazepine, phenytoin, efavirenz,</td><td>The following drugs are noted in the irinotecan prescribing information as interacting with irinotecan:
• Strong CYP3A4 inducers, e.g., St. John’s Wort, CYP3A4 inducing anticonvulsants (phenytoin, phenobarbital, and carbamazepine), rifampin, rifabutin, rifapentine
• Strong CYP3A4 inhibitors, e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole
• Weak to moderate CYP3A4 inhibitors, e.g., troleandomycin, erythromycin, diltiazem, verapamil
• Strong UGT1A1 inhibitors, e.g., atazanavir, gemfibrozil, indinavir, ketoconazole</td></tr>
</table>

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		and nevgirapine) of CYP2C8 or CYP3A. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. No live attenuated vaccines should be given to patients randomized to any arm of the study (e.g., yellow fever vaccine and polio virus vaccine). Refer to the country specific package inserts of 5-FU, leucovorin, oxaliplatin, nab-paclitaxel, or gemcitabine for any other drug interactions.	Treatment with these agents and any others that interact with irinotecan, 5-FU**, or** oxaliplatin should be avoided wherever possible. Because 5-FU interacts with warfarin, caution should be exercised if concomitant use is necessary. No live attenuated vaccines should be given to patients of the study (e.g., yellow fever vaccine and polio virus vaccine). Refer to the country specific package inserts of 5-FU, leucovorin, or oxaliplatin for any other drug interactions.
54	7.1.2	Patients who are confirmed to meet all inclusion and exclusion criteria will be enrolled in Part 1 and randomized via an IWRS in Part 2. The first dose (Cycle 1 Day 1) must be given within 7 days of enrollment/randomization.	Patients who are confirmed to meet all inclusion and exclusion criteria will be enrolled in **the study** and **receive** the first dose (Cycle 1 Day 1).
54-55	7.2.3	The Eastern Cooperative Oncology Group (ECOG) Performance Status will be obtained at Screening and within 72 hours of enrollment/randomization by the Investigator or his/her designee via questioning of the patient about their functional capabilities. Additionally, Karnofsky Performance Status (KPS) will be recorded at Screening and within 72 hours of enrollment/randomization.	The Eastern Cooperative Oncology Group (ECOG) Performance Status will be obtained at Screening, and within 72 hours **prior to first dose if first dose occurs more than 72 hours post screening**, by the Investigator or his/her designee via questioning of the patient about their functional capabilities. Additionally, Karnofsky Performance Status (KPS) will be recorded at Screening, and within 72 hours **prior to first dose if first dose occurs more than 72 hours post screening**.
55	7.2.4	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 In Part 2, patients randomized to Arm 2 will be enrolled in a QTc study evaluating sequential collection of ECGs. For these patients, ECG readings should be collected as outlined in Appendix 5.	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 **(see Section 6.5.2 for QTc in relation to diarrhea).**

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55	7.2.5		*Added text:* **Patients who continue infusion of 5-FU in home settings for the extended durations during the study, should keep a record of date/time of infusion start and stop and report any adverse events to the site. The Investigator or medically qualified person should call the patients who are discharged home for extended infusions to record the start and stop date/time for infusion and to assess adverse events reported by the patient (see Section 6.2.4.1).**
55	7.2	7.2.7 EORTC-QLQ-C30 and EQ-5D-5L (Part 2 Only) Health-related quality of life (HRQL) will be assessed by the EORTC-QLQ-C30 and EQ-5D-5L instruments. The EORTC-QLQ-C30 is a reliable and widely used measure of the quality of life of cancer patients in multicultural clinical research settings. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included. EQ-5D is a generic, preference-based measurement of HRQL. The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and unable to do. Patients will be required to complete both questionnaires at timepoints outlined in the Schedule of Assessments. On days that the patient is to receive study drug, assessments should be completed prior to study drug administration. Only those patients for whom validated translations of the questionnaires are available will be required to complete the questionnaire.	*Deleted section*

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<tr><td>55</td><td>7.3</td><td></td><td>Laboratory assessments required for screening and enrolment eligibility can be performed locally for evaluating patient eligibility and enrolment only.</td></tr>
<tr><td>56</td><td>7.3.5</td><td>Whole blood, serum and plasma will be collected to potentially identify factors that may correlate with tumor response, sensitivity or resistance to nal-IRI, and nal-IRI PK.</td><td>Archived tissue samples, whole blood, serum and plasma will be collected to potentially identify factors that may correlate with tumor response, sensitivity or resistance to nal-IRI, and nal-IRI PK.</td></tr>
<tr><td>56</td><td>7.3.7</td><td>7.3.7.2 Arm 2

Patients who are randomized to Arm 2 will undergo collection of blood samples in order to assess the relationship between blood levels of nal-IRI, SN-38 and 5-FU and ECG findings. Directions for collecting, processing and shipping the PK plasma samples can be found in the study manual. PK samples will be collected in Cycle 1 only as outlined in Table 16 below.

Table 16: Summary of PK Timepoints for Arm 2
<table>
<tr><th>Sample</th><th>Time-point</th><th>Window</th><th>Number of Draws[a]</th></tr>
<tr><td>1</td><td>Pre-dose Day 1</td><td>-24 hours</td><td>2</td></tr>
<tr><td>2</td><td>After the ECG conducted following completion of the 90 minute nal-IRI infusion on Day 1</td><td>+ 5 mins</td><td>1</td></tr>
<tr><td>3</td><td>After the ECG conducted 60 minutes into the 5-FU infusion on Day 1</td><td>+ 5 mins</td><td>2</td></tr>
<tr><td>4</td><td>After the ECG conducted 60 minutes following completion of the 46-hour 5-FU infusion on Day 3</td><td>+ 5 mins</td><td>1</td></tr>
<tr><td>5</td><td>Pre-dose Day 15</td><td>-24 hours</td><td>2</td></tr>
<tr><td>6</td><td>After the ECG conducted following completion of the nal-IRI infusion on Day 15</td><td>+ 5 mins</td><td>1</td></tr>
</table></td><td>Deleted section</td></tr>
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<table>
<tr><th colspan="2">Version Date</th><th colspan="2">29 SEPTEMBER 2017 (VERSION 5.0)</th><th>11 APRIL 2018 (VERSION 6.0)</th></tr>
<tr><th>Page</th><th>Section</th><th colspan="2">WAS</th><th>IS</th></tr>
<tr><td></td><td></td><td colspan="2"><table>
<tr><td>7</td><td>After the ECG conducted 60 minutes into the 5-FU infusion on Day 15</td><td>+ 5 mins</td><td>2</td></tr>
<tr><td>8</td><td>After the ECG conducted following completion of the 46-hour 5-FU infusion on Day 15</td><td>+ 5 mins</td><td>1</td></tr>
</table>
[a] The number of draws corresponds to the number of analytes that will be measured; for example, sample #3 at the 60 minute mark of the 5-FU infusion will be used to measure nal-IRI and 5-FU.</td><td></td></tr>
<tr><td>57-58</td><td>8</td><td colspan="2">See below</td><td>See below</td></tr>
</table>

Section 8 WAS

Procedure	Screening Phase	Treatment Phase								Follow Up Phase	
	-28d	Cycle 1[21]				Additional Cycles[21]			Every 8w after 1st dose	End of Treatment Visit[22]	Every 2 months from EoT Follow-up visit
		D1	D3	D8	D15	D1	D8	D15			
Informed consent	X										
Medical history	X[1]										
Demographics	X[1]										
Vital signs	X[2]	X		X	X	X		X		X	
ECOG PS	XX[2, 26]	X				X				X	
KPS PS	XX[2, 27]										
EORTC-QLQ-C30[9]	X[2]	X[3]				X[3]					
EQ-5D-5L[9]	X[2]	X[3]				X[3]				X	
CBC[4]	X[2]	X		X	X	X	X	X		X	
Serum chemistry[4,]	X[2, 28]	X		X	X	X		X		X	
CA19-9	X[2]								X[19]	X[20]	
UGT1A1*28	X[2, 5]										
Pregnancy test	X[2]	X				X				X	
ECG[6]	X[1,7]	X[25]			X[25]					X	
Archived slides[8]	X										
Randomization[9]	X[2]										
Plasma for PK[10]		X[11]	X[12]	X[13]	X[14]					X	
Biomarker analysis[15, 14]		X[15]				X				X	
Concomitant meds and procedures	X[1]	X	X	X	X	X	X	X		X	
Arms 1 & 2 dosing[16]		X			X	X		X			
Arm 3 dosing[16]		X		X	X	X	X	X			
AE / Hospitalization assessment & reporting	X[17]	X	X	X	X	X	X	X		X	
Disease evaluation[18]	X[1]								X[19]	X[20]	X[23]
Overall Survival											X[24]

[1] Procedures to be completed within 28 days of 1st dose of study drug
[2] Procedures to be completed within 7 days of 1st dose of study drug
[3] HRQL questionnaires must be completed before study treatment administration
[4] After screening, samples should be obtained within 2 days from scheduled date of collection
[5] Result not required prior to enrollment in the study or prior to receiving the initial dose of nal-IRI
[6] To be repeated as clinically indicated during the study
[7] Two independent readings at least 1 minute apart
[8] Collection of archived tumor block or paraffin embedded slides is required, if available
[9] Part 2 only
[10] PK sampling will only be collected from patients enrolled in Arm 1 (Part 1) or randomized to Arm 1 or Arm 2 in Part 2

[11] Samples collected at the following timepoints in Arm 1: pre-dose (within 24 hours prior to nal-IRI infusion); at the end of the nal-IRI infusion (+30 mins) and at the end of the oxaliplatin infusion (+5 mins). Samples collected at the following timepoints in Arm 2: pre-dose nal-IRI infusion, after the ECG conducted following completion of the 90 minute nal-IRI infusion, after the ECG conducted 60 minutes into the 5-FU infusion. All samples will be collected within 5 minutes after completion of the ECG recordings.

[12] In Arm 1, sample collected within 2 hours *prior* to the completion of the 5-FU infusion. In Arm 2, sample collected after the ECG conducted 60 minutes following completion of the 5-FU infusion.

[13] Sample collected +168 hours/7 days after the completion of the nal-IRI infusion (±24 hours) in Arm 1 only.

[14] In Arm 1, sample collected just prior to dosing with nal-IRI (within 24 hours). Samples collected at the following timepoints in Arm 2: pre-dose nal-IRI infusion, after the ECG conducted following completion of the 90 minute nal-IRI infusion, after the ECG conducted 60 minutes into the 5-FU infusion on Day 15, and after the ECG conducted 60 minutes following completion of the 5-FU infusion (Day 17). All samples will be collected within 5 minutes after completion of the ECG recordings.

[15] Blood will be collected for biomarker analyses: plasma samples will be collected at all timepoints; additionally, whole blood and serum samples will be collected on Cycle 1 Day 1 only

[16] Study drug administration should occur ±2 days from scheduled date of administration

[17] Adverse events that occur during screening should be documented as pre-existing conditions; only SAEs that are felt by the Investigator to be directly related to a study procedure should be reported during screening.

[18] Disease evaluation according to RECIST v. 1.1 (see Section 7.2.6)

[19] Disease evaluations and CA19-9 should be done every 8 weeks (± 7 days) after 1st dose

[20] Unless completed in the prior 8 weeks

[21] All cycles are 28-day cycles, unless modified due to toxicity

[22] The End of Treatment (EoT) Follow-Up visit should occur 30 days (± 14 days) after last dose

[23] For patients who discontinue the study for reasons other than radiologically confirmed disease progression only (e.g. patients who are removed due to adverse events), imaging studies should be continued until documented progression of disease per RECIST v1.1 (see Section 7.2.6).

[24] Follow-up contacts should be made every 8 weeks (± 7 days) until death or study completion; data collected should include overall survival status as well as subsequent treatment information.

[25] In Arm 2, ECG recordings will be collected via Holter monitor as outlined in Appendix 5 at the following timepoints: Cycle 1, Day 1: -30, -20 and -10 minutes pre-dose nal-IRI, immediately following nal-IRI infusion, immediately following the LV infusion, 60 minutes after beginning the 5-FU infusion and 60 minutes after completion of the 46-hour 5-FU infusion. Cycle 1, Day 15: -10 minutes pre-dose nal-IRI, immediately following nal-IRI infusion, immediately following the LV infusion, 60 minutes after beginning the 5-FU infusion and 60 minutes after completion of the 46-hour 5-FU infusion. Patients must be in a supine/semi-recumbent resting position for 10 minutes prior to collection times.

[26] ECOG to be performed at Screening and within 72 hours of enrollment/randomization. ECOG assessment requires determination by two independent assessors. In the case of a discrepancy between the 2 assessments, the one with a lower score will be selected at each assessment.

[27] KPS to be performed at Screening and within 72 hours of enrollment/randomization. KPS assessment requires determination by two independent assessors. In the case of a discrepancy between the 2 assessments, the one with a lower score will be selected at each assessment.

[28] Serum albumin needs to be collected at Screening Visit and within 72 hours prior to enrollment/ randomization to confirm exclusion criteria ‘p’ (both labs at screening and prior to enrollment/randomization may be confirmed locally) (Section 5.2).

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Procedure	Screening Phase	Treatment Phase								Follow Up Phase	
	-28d	Cycle 1[19]				Additional Cycles[19]			Every 8w after 1st dose	End of Treatment Visit[18]	Every 2 months from EoT Follow-up visit
		D1	D3	D8	D15	D1	D8	D15			
Informed consent	X										
Medical history	X[1]										
Demographics	X[1]										
Vital signs	X[2]	X		X	X	X		X		X	
ECOG PS	XX[2, 23]	X				X				X	
KPS PS	XX[2, 24]										
CBC[4]	X[2]	X		X	X	X	X	X		X	
Serum chemistry[4]	X[2, 25]	X		X	X	X		X		X	
CA19-9	X[2]								X[17]	X[20]	
UGT1A1*28	X[2, 5]										
Pregnancy test	X[2]	X				X				X	
ECG[6]	X[1,7]									X	
Archived slides[8]	X										
Plasma for PK		X[9]	X[10]	X[11]	X[12]					X[26]	
Biomarker analysis[12, 13]		X[13]				X				X	
Concomitant meds and procedures	X[1]	X	X	X	X	X	X	X		X	
Dosing[14]		X			X	X		X			
AE / Hospitalization assessment & reporting	X[15]	X	X	X	X	X	X	X		X	
Disease evaluation[16]	X[1]								X[17]	X[18]	X[21]
Overall Survival											X[22]

[1] Procedures to be completed within 28 days of 1st dose of study drug
[2] Procedures to be completed within 7 days of 1st dose of study drug
[3] HRQL questionnaires must be completed before study treatment administration
[4] After screening, samples should be obtained within 2 days from scheduled date of collection
[5] Result not required prior to enrollment in the study or prior to receiving the initial dose of nal-IRI
[6] To be repeated as clinically indicated during the study
[7] Two independent readings at least 1 minute apart
[8] Collection of archived tumor block or paraffin embedded slides is required, if available
[9] Samples collected at the following timepoints: pre-dose (within 24 hours prior to nal-IRI infusion); at the end of the nal-IRI infusion (+30 mins) and at the end of the oxaliplatin infusion (+5 mins).
[10] Sample collected within 2 hours *prior* to the completion of the 5-FU infusion.
[11] Sample collected +168 hours/7 days after the completion of the nal-IRI infusion (±24 hours).
[12] Sample collected just prior to dosing with nal-IRI (within 24 hours).
[13] Blood will be collected for biomarker analyses: plasma samples will be collected at all timepoints; additionally, whole blood and serum samples will be collected on Cycle 1 Day 1 only.
[14] Study drug administration should occur ±2 days from scheduled date of administration
[15] Adverse events that occur during screening should be documented as pre-existing conditions; only SAEs that are felt by the Investigator to be directly related to a study procedure should be reported during screening.
[16] Disease evaluation according to RECIST v. 1.1 (see Section 7.2.6)

[17] Disease evaluations and CA19-9 should be done every 8 weeks (± 7 days) after 1st dose
[18] Unless completed in the prior 8 weeks
[19] All cycles are 28-day cycles, unless modified due to toxicity
[20] The End of Treatment (EoT) Follow-Up visit should occur 30 days (± 14 days) after last dose
[21] For patients who discontinue the study for reasons other than radiologically confirmed disease progression only (e.g. patients who are removed due to adverse events), imaging studies should be continued until documented progression of disease per RECIST v1.1 (see Section 7.2.6).
[22] Follow-up contacts should be made every 8 weeks (± 7 days) until death or study completion; data collected should include overall survival status as well as subsequent treatment information.
[23] ECOG to be performed at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening. ECOG assessment requires determination by two independent assessors. In the case of a discrepancy between the 2 assessments, the one with a lower score will be selected at each assessment.
[24] KPS to be performed at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening. KPS assessment requires determination by two independent assessors. In the case of a discrepancy between the 2 assessments, the one with a lower score will be selected at each assessment.
[25] Serum albumin needs to be collected at Screening, and within 72 hours prior to first dose if first dose occurs more than 72 hours post screening to confirm exclusion criteria ‘p’ (both labs at screening and prior to first dose may be confirmed locally) (Section 5.2).
[26] Sample to be collected within 5 minutes after ECG recording

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62	10.4	Part 1 and Part 2 will be analyzed separately, according to safety and efficacy parameters. Patient populations defined for this study are described below: • Intent-to-Treat (ITT) population (Part 2 only): This population includes all randomized patients. Patients will be analyzed according to the randomized arm. • Safety (SAF) population: o Part 1: The Part 1 safety population includes patients receiving at least one dose of any study drug o Part 2: The Part 2 safety population includes patients receiving at least one dose of any study drug. The SAF population will be summarized according to arm actually received. • EQ-5D-5L population (Part 2 only): Treated patients, defined as patients who received at least one dose of study treatment, that have provided baseline and at least 1 post-baseline assessment for EQ-5D. • EORTC-QLQ-30 population (Part 2 only): Treated patients, defined as patients who received at least one dose of study treatment, that have provided baseline and at least 1 post-baseline assessment for EORTC-QLQ-30. • PK Population: The PK population will include all nal-IRI treated patients with at least one post-study drug PK assessment.	Patient populations defined for this study are described below: • Safety (SAF) population: The safety population includes patients receiving at least one dose of any study drug • PK Population: The PK population will include all nal-IRI treated patients **who received at least 1 dose and who have at least 1 plasma concentration and no major protocol deviations affecting PK variables**.

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62	10.5	Study populations (enrolled, safety, PK) will be summarized and displayed as frequencies. Disposition of patients will be summarized including patients screened, randomized, treated, and discontinued.	Study populations (safety, PK) will be summarized and displayed as frequencies. Disposition of patients will be summarized including patients screened, treated, and discontinued.
17, 63	Synopsis, 10.6	In the assessments of efficacy of Part 2, each nal-IRI-containing arm will be compared to the control arm. Efficacy comparisons will use stratified analyses, incorporating randomization strata. Each comparison will be use 0.10 level one-sided testing to evaluate whether the nal IRI containing arm improves the efficacy parameter. Confidence intervals will be presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals will not be adjusted for multiple comparisons and consequently the experiment-wise type I error may be greater than the 0.10 level. The primary efficacy comparisons will be based on the ITT population, which will include all randomized patients.	*Deleted text*
17, 63	Synopsis, 10.6	Tumor evaluation will be measured according to RECIST v1.1. For each patient, progression free survival time will be determined as the time from randomization (for patients in Part 1, the reference start time will be date of first study drug) to the first documented radiographical progression of disease (PD), per investigator using RECIST 1.1, or death from any cause, whichever comes first.	**Efficacy analyses will be performed on Safety population.** Tumor evaluation will be measured according to RECIST v1.1. For each patient, progression free survival time will be determined as the time from the date of first study drug to the first documented radiographical progression of disease (PD), per investigator using RECIST 1.1, or death from any cause, whichever comes first.
17, 63	Synopsis, 10.6	For Part 2, a primary analysis will be conducted when there are at least 70 PFS events for each comparison to the control arm. A subsequent analysis for PFS and other endpoints will be performed when PFS events have occurred in at least 120 (i.e. 80% of randomized patients) patients.	*Deleted text*

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17, 63	Synopsis, 10.6	***Primary Efficacy Analysis*** PFS will be descriptively summarized for each dose level cohort (Part 1) and treatment arm (Part 2) using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits will be presented. For Part 2, PFS of each nal-IRI-containing arm will be compared to the control arm. Hypothesis tests will be conducted for differences in PFS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models. ***Secondary Efficacy Analyses*** Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from enrollment (Part 1) or randomization (Part 2). Overall Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. For Part 1 and Part 2, estimates of overall response rate and its corresponding 95% CI will be calculated for each dose level cohort (Part 1) and treatment arm (Part 2). For Part 2, ORR of each nal-IRI-containing arm will be compared to the control arm. Differences in overall response rate between each nal-IRI-containing arm and control arm will be provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, will be used to compare overall response rates.	***Efficacy Analysis*** PFS will be **analyzed using Kaplan-Meier method and** descriptively summarized **at 3 months interval** for each dose level cohort. Median PFS time and corresponding 95% confidence limits will be presented. Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from **the first dose of study drug**. Overall Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. The estimates of overall response rate and its corresponding 95% CI will be calculated for each dose level cohort.

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Page	**Section**	**WAS**	**IS**
18, 63	Synopsis, 10.6	The maximum reduction (% change from baseline) in CA19-9 will be computed, including analyses by time period (up to Week 8, 16 and 24 visits). CA 19-9 response analyses will be carried out using 3 thresholds for maximum reduction: ≥ 20%, ≥50%, ≥90%. A patient without post-baseline CA19-9 measurement will be considered as a non-responder. Only patients with CA 19-9 elevated (>37 U/mL) at baseline will be included in the analysis of the CA19-9 response. For each threshold and time period, the proportion of CA19-9 response will be estimated, along with corresponding 95% confidence intervals, by treatment arm.	*Deleted text*
18, 63	Synopsis, 10.6	Overall Survival (OS) is the time from enrollment (Part 1) or randomization (Part 2) to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. OS will be descriptively summarized for each dose level cohort (Part 1) and treatment arm (Part 2) using Kaplan-Meier methodology. For Part 2, OS of each nal-IRI-containing arm will be compared to the control arm. Hypothesis tests will be conducted for differences in OS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models.	Overall Survival (OS) is the time from **the date of first study drug** to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. **Similar to PFS**, OS will be analyzed using Kaplan-Meier method and descriptively summarized for each dose level cohort.

18, 63	Synopsis, 10.6	Quality of Life Analyses Quality of life analyses will be performed using patients in the analysis populations for each quality of life instrument (EORTC-QLC-C30, EQ-5D-5L). EORTC-QLQ-30 and EQ-5D-5L results will be summarized at each visit by treatment group For each EORTC QLQ-C30 administered, scores will be computed for the following scales: • Global Health Status • Physical Functioning • Role Functioning • Emotional Functioning • Cognitive Functioning • Social Functioning • Fatigue • Nausea and vomiting • Pain • Dyspnea • Insomnia • Appetite Loss • Constipation • Diarrhea • Financial difficulties. Scoring will be carried out as described in the EORTC QLQ-C30 Scoring Manual (Fayers, Aaronson, Bjordal, Curran, & Groenvald, 2001). Linear transformations will be applied to the raw scores so that the reported score will have range 0-100 for all scales. Summary statistics will be presented for each subscale. A summary health state index value will be computed for each EQ-5D-5L assessment. Summary statistics will be presented for summary health state index. For each EQ-5D-5L attribute (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), responses will be tabulated.	*Deleted text*

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64	10.7	Details on the analyses to assess the potential of QTcF prolongation with nal-IRI treatment are provided in Appendix 5.	*Deleted text (and corresponding Appendix 5)*
64	10.9	10.9.1 Part 1 and Part 2 Arm 1 Plasma concentrations of total irinotecan, SN-38 and oxaliplatin will be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method with priors from the previously estimated (nal-IRI) or published (oxaliplatin) population PK model parameters. The model simulated exposures, e.g., C_{max}, AUC (area under the curve), will be used to examine any possible interactions between nal-IRI and oxaliplatin by comparing the least squares geometric mean ratios (LS-GMR) of drug exposures. The relationship between dose, PK, efficacy and safety endpoints will be evaluated. NONMEM®, Version 7.3, will be used to estimate individual PK parameters and simulate plasma exposures. 10.9.2 Part 2 Arm 2 Plasma concentrations of total irinotecan, SN-38 and 5-FU will be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method with priors from the previously estimated population PK models. The model simulated exposures, e.g., C_{max}, AUC (area under the curve), will be used to evaluate the relationship between dose, PK, efficacy and safety endpoints. Moreover, the potential for QTcF prolongation will be evaluated from the relationship between PK and QTcF.	Plasma concentrations of total irinotecan, SN-38, and oxaliplatin **and 5-FU in the combination therapies** will be used to characterize **corresponding** PK parameters **using a nonlinear mixed effects approach. Individual PK** parameters will be estimated if **warranted by the data. Graphical exploration will be performed to investigate any relationship between PK and pharmacodynamic endpoints. If a trend is shown, PK/PD modelling will be performed and reported separately**.

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<tr><td>64-65</td><td>10.10</td><td>Part 2 of this study will include a comparison of the progression-free survival for each lip IRI containing arm versus the control arm. In the Phase 3 MPACT study of nab-paclitaxel plus gemcitabine versus gemcitabine alone, a significant OS advantage was observed with nab paclitaxel with the median PFS of 5.5 months (compared with 3.7 months, i.e. 16 weeks, in the gemcitabine alone arm) [2]. The table below illustrates the power to detect differences in PFS between an experimental arm and the control arm with at least 70 PFS events using a one-sided comparison at an unadjusted 0.10 level of significance. If the true hazard ratio for an experimental arm relative to the control arm is 0.60, the study would have 80% power to detect an improvement with a pairwise one-sided 0.10 level test.
Table 18: Power to Detect Treatment Effect
<table>
<tr><th>Hazard ratio for PFS (experimental vs control)</th><th>Power (≥ 70 events between 2 arms for comparison)</th></tr>
<tr><td>0.75</td><td>47%</td></tr>
<tr><td>0.70</td><td>58%</td></tr>
<tr><td>0.65</td><td>70%</td></tr>
<tr><td>0.60</td><td>80%</td></tr>
<tr><td>0.55</td><td>88%</td></tr>
</table></td><td>Below text added was in the synopsis and have been added in Section 10.10.
A selected dose level cohort will be expanded to include 30 patients in total. An estimate of the DCR at Week 16 will be tabulated and summarized. The following table displays the probabilities of outcomes for DCR_{16} with n=30 as a function of the true DCR_{16}:
Table 12: Probability probabilities of outcomes for DCR16
<table>
<tr><th>True DCR_{16}</th><th>Probability observed $DCR_{16} \geq 50\%$</th><th>Probability observed $DCR_{16} \geq 55\%$</th><th>Probability observed $DCR_{16} \geq 60\%$</th></tr>
<tr><td>45%</td><td>0.36</td><td>0.14</td><td>0.07</td></tr>
<tr><td>50%</td><td>0.57</td><td>0.29</td><td>0.18</td></tr>
<tr><td>55%</td><td>0.77</td><td>0.50</td><td>0.36</td></tr>
<tr><td>60%</td><td>0.90</td><td>0.71</td><td>0.58</td></tr>
<tr><td>65%</td><td>0.97</td><td>0.87</td><td>0.78</td></tr>
<tr><td>70%</td><td>0.99</td><td>0.96</td><td>0.92</td></tr>
</table></td></tr>
</table>

70-72	13	*Three references, listed below, were deleted. References cited in the text have been updated accordingly.* [13] "Gemcitabine for injection U.S. Package Insert," 2014. [Online]. Available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020509s077lbl.pdf. [14] "ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension)," 2014. [Online]. Available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021660s040lbl.pdf. [39] Sarapa, N., Britto, M.R. Challenges of characterizing proarrhythmic risk due to QTc prolongation induced by nonadjuvant anticancer agents. Expert Opin Drug Saf. vol. 7, no. 3, pp 305-318, 2008.	*The five following new references were added to the reference list. References cited in the text have been updated accordingly.* [27] Iyer L1, Das S, Janisch L, Wen M, Ramírez J, Karrison T, Fleming GF, Vokes EE, Schilsky RL, Ratain MJ. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J. 2002;2(1):43-7. [28] Stewart CF, Panetta JC, O'Shaughnessy MA, Throm SL, Fraga CH, Owens T, Liu T, Billups C, Rodriguez-Galindo C, Gajjar A, Furman WL, McGregor LM. UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. J Clin Oncol. 2007 Jun 20; 25(18):2594-600. [29] Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst. 2007 Sep 5; 99(17):1290-5. [30] Toffoli G, Cecchin E, Corona G, Russo A, Buonadonna A, D'Andrea M, Pasetto LM, Pessa S, Errante D, De Pangher V, Giusto M, Medici M, Gaion F, Sandri P, Galligioni E, Bonura S, Boccalon M, Biason P, Frustaci S. The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J Clin Oncol. 2006 Jul 1; 24(19):3061-8. [31] Roy AC, Park SR, Cunningham D, Kang YK, Chao Y, Chen LT, Rees C, Lim HY, Tabernero J, Ramos FJ, Kujundzic M, Cardic MB, Yeh CG, de Gramont A. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Ann Oncol. 2013 Jun; 24(6):1567-73.
74	14	Bin Zhang.	**Fiona Maxwell**

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		Senior Medical Development Director Oncology and Endocrinology Ipsen Bioscience, Inc.	Medical Development Director Oncology **Ipsen Bioinnovation**
76	Appendix	Appendix 2 Proposed Algorithm for Diarrhea Management: Reference in the footnote was incorrect [30]	Reference in the footnote has been corrected: [36]
79	Appendix	Appendix 5 QTc Sub-study Protocol (see at the end of this summary of changes)	*Deleted appendix*

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	MM-398-07-02-03	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Version 6.0, 11 April 2018**	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
OBJECTIVE(S) OF PROTOCOL AMENDMENT	• To remove the comparative Part 2 (regimens: nal-IRI + 5FU/LV and nab-paclitaxel + gemcitabine) and all related information (e.g., comparison versus nab-paclitaxel plus Gemcitabine; Arms 1, 2 and 3, randomization). • To add or modify inclusion criteria • To add, remove or modify exclusion criteria • To add clinical data in UGT1A1*28 homozygous patients • To update dose modification rules • To modify granulocyte Colony Stimulating Factors • To specify treatment infusion of 5-FU continued at home • To remove QTcF assessments and Appendix 5 (QT specific), which were specific to Part 2 • Other changes were made for clarification or correction	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐ *(tick one)*

Appendix 5: QTc Sub-study Protocol *(Deleted in Protocol Version 6.0)*

The objective of the QTc sub-study is to evaluate the potential of QTcF prolongation with nal-IRI treatment. Patients randomized to Arm 2 in Part 2 of the study will be enrolled in a QTc sub-study. For these patients, ECGs should be collected following the schedule outlined below. For each collection point, patients should be in a supine/semi-recumbent, resting position for at least 15 minutes. Recording should begin 10 minutes prior to the nominal collection time, as only the last 5 minutes of each recording will be used for analysis. Moreover, PK samples will be collected within 5 min after each ECG collections as specified in **Table A** and **Figure A**.

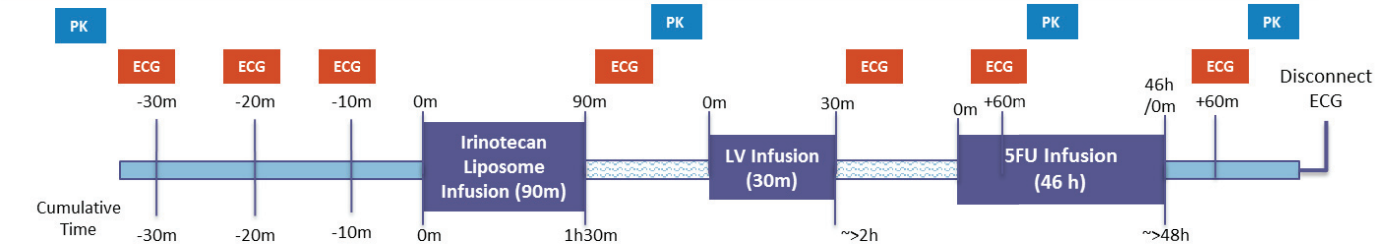
Table A: Schedule of ECG and PK Sampling Times

Cycle/Day	Number of ECG Readings	ECG Time Points	PK Collection
Cycle 1 Day 1	3	Pre-dose -30, -20 and -10 minutes	Yes
Cycle 1 Day 1	1	Post-dose nal-IRI	Yes
Cycle 1 Day 1	1	Post-dose LV infusion	No
Cycle 1 Day 1	1	60 minutes after initiating 5-FU infusion	Yes
Cycle 1 Day 3	1	60 minutes after completing 5-FU infusion	Yes
Cycle 1 Day 15	1	Pre-dose -10 minutes	Yes
Cycle 1 Day 15	1	Post-dose nal-IRI	Yes
Cycle 1 Day 15	1	Post-dose LV infusion	No
Cycle 1 Day 15	1	60 minutes after initiating 5-FU infusion	Yes
Cycle 1 Day 17	1	60 minutes after completing 5-FU infusion	Yes

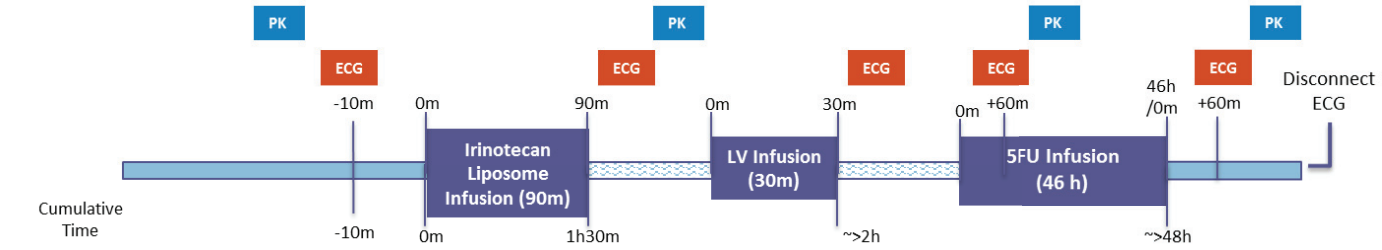
Figure A: Timing of ECG and PK Sampling in Arm 2

Note: Post dose PK must be done <u>after</u> ECG recording.
(Patients must be supinely resting for at least 10 minutes prior to and 5 minutes after each ECG timepoint)

Cycle 1 Day 1	Pre-infusion			MM398 Infusion (90 min)	End of MM398 Infusion	LV infusion (30min)	End of LV Infusion	5FU infusion (46 hrs)	End of 5FU Infusion
	-30min	-20 min	-10min					+60min	+60min
PK	X (2 draws)- no ECG pairing required				X (1 draw)			X (2 draw)	X (1 draw)
ECG	X	X	X		X		X	X	X



Cycle 1 Day 15	Pre-infusion			MM398 Infusion (90 min)	End of MM398 Infusion	LV infusion (30min)	End of LV Infusion	5FU infusion (46 hrs)	End of 5FU Infusion
	-30min	-20 min	-10min					+60min	+60min
PK	X (2 draws)- no ECG pairing required				X (1 draw)			X (2 draw)	X (1 draw)
ECG			X		X		X	X	X



The 12-lead Holter and ECG equipment will be supplied and supported by iCardiac Technologies, Inc. All ECG data will be collected using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12 lead digital recorder. The continuous 12-lead digital ECG data will be stored on SD memory cards. ECGs to be used in the analyses will be read centrally by iCardiac Technologies, Inc.

The following principles will be followed in iCardiac's core laboratory:

- ECG analysts are blinded to the patient and visit allocation
- Baseline and on-treatment ECGs for a particular patient will be over-read on the same lead and will be analyzed by the same reader.
- The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire patient data set.

A description of ECG extraction and interval measurements with the High Precision QT technique is given in the iCardiac's ECG manual.

Planned Statistical Methods

Detailed plans for the statistical methods of the sub-study will be provided in a statistical analysis plan which will be finalized prior to database lock.

1. Determination of Sample Size

Evaluation of QTcF will be performed in approximately 20 patients with evaluable QT and PK samples.

The sample size of the QT sub-study is not based on a formal power calculation but is based on what is deemed feasible in this patient population. An estimate of the power can be obtained by looking at one test (one sided, one group), with a threshold of the QT effect (ΔQTcF) of 20 ms and variability of ΔQTcF that is assumed to be substantially higher than in healthy volunteer studies. The table below gives the power of a test for non-inferiority (single group) against a threshold of 20 ms based on 20 patients at a one-sided 5% level assuming various values for the SD of the change from baseline. The threshold of 20 ms was selected based on regulatory feedback on other oncology programs [39]. With 20 evaluable patients, the probability that the upper bound of the 90% confidence interval to be less than 20 ms as a function of assumed underlying effects and standard deviation of the ΔQTcF is provided in **Table B** which show high precision in evaluating QTcF effects.

Table B: Power to exclude a QT effect (ΔQTcF) exceeding 20 ms

Assumed Underlying Effect	SD of ΔQTcF	Power to Exclude 20 ms QTc Effect[a]
0	12	1.00
0	15	1.00
0	20	1.00
0	25	0.96
3	12	1.00
3	15	1.00
3	20	0.98
3	25	0.90
5	12	1.00
5	15	1.00
5	20	0.94
5	25	0.83
10	12	0.97
10	15	0.89
10	20	0.70
10	25	0.53

[a] The upper bound of the 90% confidence interval will fall below 20 ms

2. Analysis Populations

Safety Set: consists of all patients enrolled in the sub-study, who received at least one dose of study drug.

QTc Analysis Set: consists of all patients in the safety set who had ECG measurements at baseline as well as on-treatment data with at least 1 post-dose time point with a QTcF value.

Pharmacokinetic (PK) Analysis Set: consists of all patients enrolled in the sub-study, which received the study drug and have at least one valid PK concentration measurement for study drug.

PK/QTc Analysis Set: contains all patients in the QTc analysis and the PK analysis sets with at least one pair of post-dose PK and QTc data from the same timepoint.

3. General Methodology

All statistical analysis of the sub-study will be performed using the statistical software SAS for Windows Version 9.3 (SAS Institute, Inc., Cary, NC). Data collected from all patients

enrolled in the sub-study will be presented in data listings. Both absolute values and change from baseline for each patient will be given where applicable. All continuous data will be listed with the same precision as will be presented in the database. Data listings will be sorted by treatment, patient ID, and timepoint. Missing values will be represented by an empty cell and no imputation will be made.

Continuous data will be summarized in tables using missing data count, mean, median, range, standard deviation (SD), standard error (SE), and 90% 2-sided confidence interval (CI; based on a t-distribution if not otherwise stated) by treatment and timepoint. All continuous data will be rounded to the nearest tenth. Categorical data (including the missing data category) will be summarized by treatment and timepoint using counts and percentages. Percentages will be rounded up or down to next integer percentage. Population counts for the sub-study will be used as the denominator in the calculation of percentages unless otherwise specified.

4. Statistical Procedures and Descriptive Summaries

The primary analysis to evaluate the potential of QTcF prolongation is based on the exposure-response analysis with the objective to exclude a QT effect (ΔQTcF) exceeding 20 ms. Additional analyses, including by-timepoint and categorical analyses, will be used as sensitivity analyses.

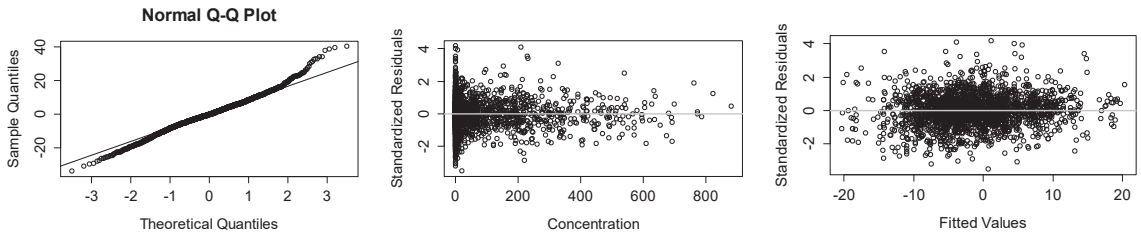
Exposure-Response Analysis: The relationship between nal-IRI, SN-38 and 5-FU plasma concentrations and ΔQTcF (change-from-baseline QTcF) will be investigated by a linear mixed effects modeling approach, that is:

$$\Delta QTcF \sim Intercept + C1 + C2 + C3$$

with C1 is the concentration of total irinotecan, C2 is that of SN-38 and C3 is that of 5-FU. Any concentrations below BQL will be set to 0. Patients will be included in the model as a random effect for both intercept and slope, when applicable. Starting from this model, simpler models will be explored by removing those concentrations whose effects are not significant. In particular, a model without C3 (5-FU) will be explored, since this drug has a very short half-life.

The model with the lowest AIC (the Akaike information criterion) will be used for predicting ΔQTcF. For each analyte (a) included in this model, a prediction will be made at the geometric mean Cmax of this analyte and the geometric mean concentration of the other analytes observed at Tmax of analyte (a). For each prediction, the predicted effect and its 2-sided 90% CI for ΔQTcF will be obtained.

Appropriateness of a linear model: To assess the appropriateness of a linear model, normal QQ-plots for the residuals and plots of weighted residuals vs. concentration and vs. fitted values will be produced. Examples of these plots are shown below:



In addition, a model with interactions and quadratic terms in concentration will be fitted. If there is an indication that a linear model is inappropriate or there is a relevant interaction between drugs, further exploratory modelling will be performed. This may include, but is not limited to:

- replacing the concentration C in the primary model by a log-transformation of C, e.g., $\log(C/C_0)$, where C_0 is the limit of quantification of the assay used to determine C and all values below C_0 are replaced by C_0 (i.e., $\log[C_0/C_0] = 0$).
- fitting a nonlinear model such as an Emax model.

The exposure-response analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

By-Timepoint Analysis:

In addition to the summaries described in Section 3, a model based by-timepoint analysis will be performed. The analysis for QTcF will be based on a linear mixed-effects model with ΔQTcF as the dependent variable, baseline QTcF as covariate, and time (categorical) as factor. An unstructured covariance matrix will be specified for the repeated measures at post-dose timepoints within patient. If the model with unstructured covariance matrix fails to converge, other covariance matrix such as compound symmetry can be considered. For each timepoint, the LS-means will be given together with SE and 90 % CI. For change-from-baseline HR, PR, QRS, QT and RR, the same model will be used as described for QTcF and the same results will be tabulated. The By-Timepoint-Analysis will be interpreted descriptively.

The presence of hysteresis, i.e. a time-lag between Cmax and the largest QTc effect, will be graphically evaluated on an exploratory basis.

Categorical Analysis: The analysis results for categorical outliers and T-wave morphology will be summarized in frequency tables with counts and percentages for both number of patients and number of timepoints. For categorical outliers, the number (percentage) of patients as well as timepoints with increases in QTcF from baseline of >30 and >60 msec and absolute QTcF values >450, >480, and >500 msec; increase in PR interval from baseline >25% and a PR interval >200 msec; increase in QRS interval from baseline >25% and a QRS interval >120 msec; decrease in HR from baseline >25% and a HR <50 bpm; and increase in HR from baseline >25% and a HR >100 bpm will be determined by each treatment group, respectively. For T-wave morphology, the analysis will be focused on the treatment-emergent changes. The T-wave morphology categories are described as follows:

Category	Description
Normal T wave (+)	Any positive T wave not meeting any criterion below
Flat T wave	T amplitude ≤1 mm (either positive or negative), including flat isoelectric line
Notched T wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T wave
Biphasic	T wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive/negative and negative/positive and polyphasic T waves included)
Normal T wave (-)	T amplitude is negative, without biphasic T wave or notches
Notched T wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T wave

All outliers will be summarized on the basis of incidence rates. A patient will be counted only once for a particular outlier event if the patient experiences more than one incidence of that event.

Appendix 8: Summary of Changes: 11 April 2018 (version 6.0) to 27 September 2019 (version 7.0)

STUDY NUMBER:	MM-398-07-02-03
PROTOCOL TITLE:	**A RANDOMIZED, OPEN-LABEL PHASE 2 STUDY OF NANOLIPOSOMAL IRINOTECAN (NAL-IRI)-CONTAINING REGIMENS *VERSUS* NAB-PACLITAXEL PLUS GEMCITABINE IN PATIENTS WITH PREVIOUSLY UNTREATED, METASTATIC PANCREATIC ADENOCARCINOMA**
AMENDED PROTOCOL VERSION NUMBER & DATE	Version 7.0, 27 September 2019

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED: Underlined text in "Was" indicates deleted text; Bold text in "Is" indicates new text. This does not apply to tables.

Version Date		11 APRIL 2018 (VERSION 6.0)	27 SEPTEMBER 2019 (VERSION 7.0)
Page	**Section**	**WAS**	**IS**
16	Synopsis		Length of Study **Following fulfilment of analysis requirements for the primary and/or secondary endpoints, the sponsor may elect to transition patients that are still receiving treatment or are being followed for OS to an extension phase of the study.**
65	11	Following fulfillment of analysis requirements for the primary and/or secondary endpoints, the Sponsor may elect to close the study. At that time, all patients receiving treatment will be permitted to transition into the extension phase of the study, and will continue to receive treatment until disease progression, death, unacceptable study drug related toxicity, patient refusal, or start of any new anticancer treatment, whichever occurs first (see Section 5.3 for other discontinuation criteria). Central collection of data will not be required for patients entering the extension phase of the study; only serious adverse events will be collected. Investigators may perform standard procedures and tests needed to treat and evaluate patients;	Following fulfillment of analysis requirements for the primary and/or secondary endpoints, the Sponsor may elect to **transition patients that are still receiving treatment or are being followed for OS to an extension phase of the study.** **Patients will continue to be followed for OS every 4 months.** **Patients still** receiving treatment will continue to receive **this** until disease progression, death, unacceptable study **medication** related toxicity or **withdrawal of consent** (see Section 5.3 for other discontinuation criteria). **For patients receiving treatment in the extension phase of the study only OS and treatment-related SAEs will be**

Version Date		11 APRIL 2018 (VERSION 6.0)	27 SEPTEMBER 2019 (VERSION 7.0)
Page	**Section**	**WAS**	**IS**
		however, the results of these assessments will not be routinely reported. In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and procedures) may be requested by the Sponsor in order to evaluate the reported SAE. The patient's participation in the study extension will be completed once study treatment is discontinued. There will be no post discontinuation period in the extension phase of the protocol.	**collected in the eCRF**. In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and procedures) may be requested by the Sponsor in order to evaluate the reported SAE, **although this additional information does not need to be captured in the eCRF**. Investigators may perform standard procedures and tests needed to treat and evaluate patients; however, the results of these assessments will not be routinely reported. **The extension phase of the study will be completed once all patients have died, withdraw consent, or lost to follow-up after two attempts on OS follow-up.**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	MM-398-07-02-03	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Version 7.0, 27 September 2019**	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
OBJECTIVE(S) OF PROTOCOL AMENDMENT	• To clarify the extension part of the study will collect very limited data (only treatment-related SAEs and OS) with no study procedures apart from patients continuing on study medication for as long their treating physician feels they derive benefit.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☐ No ☒ *(tick one)*

Summary of Changes

Regarding compound MM-398, this is a Summary of Changes for Protocol MM-398-07-02-03, "*A Randomized, Open-label Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI)-containing Regimens versus nab-Paclitaxel plus Gemcitabine in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma*", from Version 1.0 to Version 2.1.

	Version No:	**Version Date**
Replaced Approved Protocol	1.0	26 Jun 2015
Current Approved Protocol	2.0	24 Mar 2016

General Changes and Note

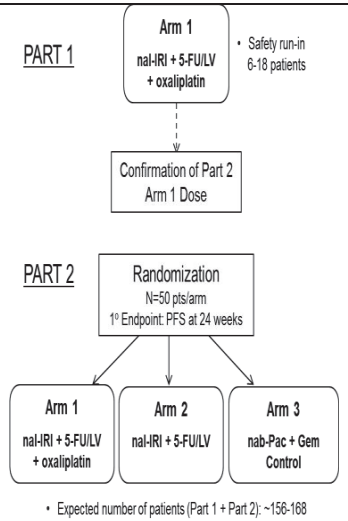
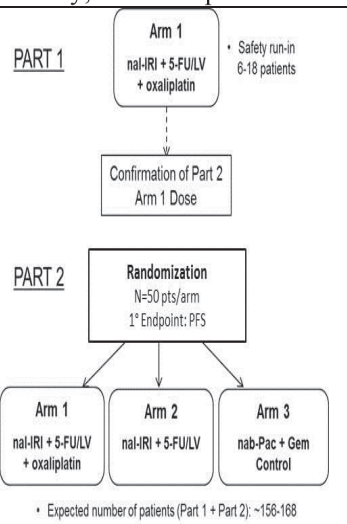
Protocol MM-398-07-02-03 is being amended to address changes to the planned statistical analyses and to incorporate the addition of electrocardiogram studies paired with time-matched pharmacokinetic sampling to assess possible changes in QTc intervals.

In addition to the two protocol changes, several administrative changes have been made.

Changes to Protocol MM-398-07-02-03 Version 1.0 to Version 2.0

Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
List of Abbreviations	N/A	QTcF: QT interval, Fridericia correction	The addition of calculations of QT interval measurement to the protocol.
Section 1.2.1.1: Nal-IRI Pre-Clinical Pharmacokinetics Section 1.2.2.1: Nal-IRI PK in Humans Section 1.3.1: Rationale for Arm 1: Nal-IRI + 5-FU/LV + Oxaliplatin	Free irinotecan	Non-liposomal irinotecan	All instances of "free irinotecan" have been changed to "non-liposomal irinotecan" to more accurately reflect irinotecan that is not encapsulated in a nanoliposome drug delivery system.
Section 2.2.1: Primary Objectives	To assess efficacy of nal-IRI-containing regimens in first-line metastatic pancreatic cancer patients compared to nab-paclitaxel + gemcitabine using the progression free survival (PFS) rate at 24 weeks	To assess efficacy of nal-IRI-containing regimens in first-line metastatic pancreatic cancer patients compared to nab-paclitaxel + gemcitabine using progression free survival (PFS)	The primary endpoint was changed to PFS to enable a more sensitive analysis of the primary endpoint analysis. Assuming a median PFS time of 5.5 months in the control arm and exponential distribution for PFS, an increase in PFS at 24 weeks from 50% to 70% implies a hazard ratio of 0.55. The amendment planned analysis of PFS has 88% power for HR=0.55. Consequently, the endpoint was changed to the more informative standard PFS endpoint.

Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
Section 2.2.2: Secondary Objectives	• To assess the efficacy of each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine using overall survival (OS), PFS, and objective response rate (ORR; CR + PR, per RECIST v1.1) • To assess tumor marker CA19-9 response in each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine • To assess health-related quality of life (HRQL) using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30) and European Quality of Life Questionnaire (EQ-5D-5L) in each arm • To compare the safety and adverse event profile between the treatment arms	• To assess the efficacy of each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine using overall survival (OS) and objective response rate (ORR; CR + PR, per RECIST v1.1) • To assess tumor marker CA19-9 response in each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine • To assess health-related quality of life (HRQL) using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30) and European Quality of Life Questionnaire (EQ-5D-5L) in each arm • To compare the safety and adverse event profile between the treatment arms • To assess the potential for QTcF prolongation with nal-IRI treatment	The primary endpoint was changed to PFS to enable a more sensitive analysis at the planned timing of the primary endpoint analysis and so this endpoint was removed from secondary endpoints. The addition of ECG readings and time-matched PK sample collections for evaluation of QTc prolongation.

Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
Section 2.2.3: Exploratory Objectives	• To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI PK, toxicity, and/or response	• To evaluate the relationship between plasma PK of nal-IRI (total irinotecan, SN-38), oxaliplatin and efficacy and safety endpoints in first-line metastatic pancreatic cancer • To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI PK, toxicity, and/or response	To more fully characterize the PK profile of the nal-IRI +5-FU/LV regimen in first-line treatment for metastatic pancreatic cancer.
Section 3.0: Study Design			Amended to reflect the change from PFS at 24 weeks to PFS.
Section 3.1: Study Design Overview (Part 2, Paragraph 1)	Part 2 will consist of an open-label, randomized, Phase 2 study where patients will be randomized to treatment (1:1:1) to either nal-IRI + 5-FU/LV + oxaliplatin, nal-IRI + 5-FU/LV,	Part 2 will consist of an open-label, randomized, Phase 2 study where patients will be randomized to treatment (1:1:1) to either nal-IRI + 5-FU/LV + oxaliplatin, nal-IRI + 5-FU/LV,	The addition of ECG readings and time-matched PK sample collections for evaluation of any possible QTc prolongation by nal-IRI in Arm 2.

Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
	or nab-paclitaxel + gemcitabine. The randomization will be stratified based on region (East Asia vs. rest of the world) and performance status (ECOG 0 vs. 1). During Part 2, a regular review of safety data will be conducted by an independent Data and Safety Monitoring Board (DSMB). The DSMB will consist of oncology and statistical experts, independent of the Sponsor. The timing of the safety reviews, and the workings of the DSMB, will be detailed in the DSMB charter. The DSMB is a precaution in the event of unanticipated toxicities, and the study will not be stopped early on the basis of differences in efficacy, therefore no prospective adjustment of the final significance levels is planned on the basis of this review.	or nab-paclitaxel + gemcitabine. The randomization will be stratified based on region (East Asia vs. rest of the world) and performance status (ECOG 0 vs. 1). Patients randomized to nal-IRI + 5-FU/LV will undergo serial ECG recordings and time-matched pharmacokinetic sampling to assess any relationship between blood levels of nal-IRI and possible changes in QTc intervals. During Part 2, a regular review of safety data will be conducted by an independent Data and Safety Monitoring Board (DSMB). The DSMB will consist of oncology and statistical experts, independent of the Sponsor. The timing of the safety reviews, and the workings of the DSMB, will be detailed in the DSMB charter. The DSMB is a precaution in the event of unanticipated toxicities, and the study will not be stopped early on the basis of differences in efficacy, therefore no prospective adjustment of the final significance levels is planned on the basis of this review.	
Section 5.1: Inclusion Criteria	f) Adequate renal function as	f) Adequate renal function as	Creatinine clearance was changed to

Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
	evidenced by serum creatinine ≤ 1.5 x ULN, and calculated clearance ≥60 mL/min/1.72 m2 for patients with serum creatinine levels above or below the institutional normal value. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); for patients with body mass index (BMI) >30 kg/m2, lean body weight should be used instead.	evidenced by serum creatinine ≤ 1.5 x ULN, and calculated clearance ≥60 mL/min/1.73 m2 for patients with serum creatinine levels above or below the institutional normal value. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); for patients with body mass index (BMI) >30 kg/m2, lean body weight should be used instead.	correct the value to the accepted standard.
Section 5.2: Exclusion Criteria	c) Known metastasis to the central nervous system. n) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 3 months following the last dose of study drug.	c) Uncontrolled CNS metastases (patients who require steroids should be on a stable or decreasing dose) n) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 4 months following the last dose of study drug.	CNS metastases, as long as they are controlled, should not be a de novo exclusion for patients with solid tumors on clinical studies. To align with the Onivyde (irinotecan liposome injection) USPI.

Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
Section 6.1.1: Description of Nal-IRI	Nal-IRI (irinotecan liposome injection, also known MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. It will be supplied in sterile, single-use vials containing 10 mL or 9.5 mL of nal-IRI at a concentration of 5 mg/mL. nal-IRI must be stored refrigerated at 2 to 8°C, with protection from light. The appearance of MM-398 is white to slightly yellow opaque liquid.	Nal-IRI (irinotecan liposome injection, also known MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. It will be supplied in sterile, single-use vials containing 10 mL of nal-IRI at a concentration of 5 mg/mL. nal-IRI must be stored refrigerated at 2 to 8°C, with protection from light. The appearance of MM-398 is white to slightly yellow opaque liquid.	To align with current investigational drug supply.
Section 6.1.1.1: Storage and Handling of Nal-IRI	Nal-IRI must be diluted prior to administration. The diluted solution is physically and chemically stable for 6 hours at room temperature (15-30°C), but it is preferred to be stored at refrigerated temperatures (2-8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2-8°C), and within 6 hours if kept at room temperature (15-30°C).	Nal-IRI must be diluted prior to administration. The diluted solution is physically and chemically stable for 4 hours at room temperature (15-25°C), but it is preferred to be stored at refrigerated temperatures (2-8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2-8°C), and within 4 hours if kept at room temperature (15-25°C).	To align with the Onivyde (irinotecan liposome injection) USPI.
Section 6.3.1: Arm 1: Nal-IRI + 5-FU/LV + Oxaliplatin	The order of the infusions to be administered in the clinic will be as follows: nal-IRI will be administered first, followed by	The order of the infusions to be administered in the clinic will be as follows: nal-IRI will be administered first, followed by	Language change to clarify the timing of administration of leucovorin.

Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
	oxaliplatin, then LV, followed by 5-FU. In Part 1, patients will receive the oxaliplatin infusion 2 hours after the completion of the MM-398 infusion. If no infusion reactions are seen, Part 2 patients can receive oxaliplatin directly after completion of the MM-398 infusion. If any grade 3 or higher infusion reactions are seen in Part 2 patients, the DSMB may elect to revert back to administration of oxaliplatin two hours after the completion of the MM-398 infusion.	oxaliplatin, then LV, followed by 5-FU. In Part 1, patients will receive the oxaliplatin infusion 2 hours after the completion of the MM-398 infusion and will receive leucovorin 30 min after oxaliplatin. If no infusion reactions are seen, Part 2 patients can receive oxaliplatin directly after completion of the MM-398 infusion and leucovorin directly after completion of oxaliplatin. If any grade 3 or higher infusion reactions are seen in Part 2 patients, the DSMB may elect to revert back to the original observation periods.	

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Section 6.3.3: Doses and Administration of Nal-IRI (Arms 1 and 2)	Nal-IRI will be administered by intravenous (IV) infusion over 90 minutes (±10 minutes) every two weeks. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days. Prior to administration, the appropriate dose of nal-IRI must be diluted in 5% Dextrose Injection solution (D5W) or normal saline to a final volume of 500 mL. Care should be taken not to use in-line filters or any diluents other than D5W or normal saline. Nal-IRI can be administered at a rate of up to 1 mL/sec (30 mg/sec).	Nal-IRI will be administered at a dose of 80 mg/m2 as an IV infusion over 90 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 2 days. Prior to administration, the appropriate dose of nal-IRI must be diluted in 5% Dextrose Injection solution (D5W) or 0.9% Sodium Chloride Injection to a final volume of 500 mL. Care should be taken not to use any diluents other than D5W or 0.9% sodium chloride.	Language change to clarify the preparation and administration of nal-IRI.
Section 6.3.4: Doses and Administration of 5-FU and Leucovorin (Arms 1 and 2)	Leucovorin should be administered prior to the 5-FU infusion (on Arm 1, leucovorin will be given concurrently with oxaliplatin, see Section 7.3.1). Actual dose of 5-FU and leucovorin to be administered will be determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.	Leucovorin should be administered prior to the 5-FU infusion (on Arm 1, leucovorin will not be given concurrently with oxaliplatin, see Section 7.3.1). Actual dose of 5-FU and leucovorin to be administered will be determined by calculating the patient's body surface area prior to each cycle. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration.	Language change to clarify the timing of leucovorin administration relative to oxaliplatin.
Section 6.7.1: Antiemetic Medications	Dexamethasone and a 5-HT3	Dexamethasone and a 5-HT3	To avoid the possible confounding

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	blocker (e.g., ondansetron or granisetron) will be administered as premedications to all patients assigned to Arm 1 and Arm 2 unless contraindicated for the individual patient. Antiemetics will also be prescribed as clinically indicated during the study period.	blocker (e.g., ondansetron or granisetron) will be administered as premedications to all patients assigned to Arm 1 and Arm 2 unless contraindicated for the individual patient. For patients randomized to Arm 2, during cycle 1 ECG monitoring, consider alternatives to 5-HT3 blockers which have been associated with QT changes. Antiemetics will also be prescribed as clinically indicated during the study period.	effects of 5-HT3 blockers during QTc monitoring.
Section 7.2.4: Electrocardiogram (ECG)	A 12 lead ECG will include a description of the cardiac rate, rhythm, interval durations and an overall impression. If ECG is abnormal, clinical significance should be indicated.	A 12 lead ECG will include a description of the cardiac rate, rhythm, interval durations and an overall impression. If ECG is abnormal, clinical significance should be indicated. In Part 2, patients randomized to Arm 2 will be enrolled in a QTc study evaluating sequential collection of ECGs. For these patients, ECG readings should be collected as outlined in Appendix 5.	Serial ECG testing added to Arm 2 to assess for possible changes in QTc intervals caused by nal-IRI.
Section 7.3.5: Biomarker Samples	Whole blood and plasma will be collected to potentially identify factors that may correlate with tumor response, sensitivity or resistance to nal-IRI, and nal-IRI PK. Examples of potential analyses include cytokine levels	Whole blood, serum and plasma will be collected to potentially identify factors that may correlate with tumor response, sensitivity or resistance to nal-IRI, and nal-IRI PK. Examples of potential analyses include	To clarify that serum samples will also be collected for biomarker analysis.

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	(e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), enzyme levels (e.g. MMP9).	cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), enzyme levels (e.g. MMP9).	
Section 7.3.7: Pharmacokinetic Assessments	8.3.7: Pharmacokinetic Assessments (Arm 1 Only) Since the combination of nal-IRI and oxaliplatin has not yet been tested in the clinic, plasma samples will be collected to determine the levels of nal-IRI and SN-38, as well as 5-FU and oxaliplatin, in Arm 1 patients. Additional analytes which may impact the pharmacokinetics of nal-IRI may also be measured from this sample. Directions for processing and shipping the PK plasma samples can be found in the study manual. The PK time points outlined in the Table 12 below will be drawn during Cycle 1 only. PK samples will be collected during Parts 1 and 2 of the study.	7.3.7: Pharmacokinetic Assessments 7.3.7.1: Arm 1 Since the combination of nal-IRI and oxaliplatin has not yet been tested in the clinic, plasma samples will be collected to determine the levels of nal-IRI and SN-38, as well as 5-FU and oxaliplatin, in Arm 1 patients. Additional analytes which may impact the pharmacokinetics of nal-IRI may also be measured from this sample. Directions for processing and shipping the PK plasma samples can be found in the study manual. The PK time points outlined in Table 12 below will be drawn during Cycle 1 only. PK samples will be collected during Parts 1 and 2 of the study.	Pharmacokinetic sampling added to Arm 2 to evaluate any relationship between blood levels of nal-IRI and possible changes in QTc intervals.

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text: Version 2.1</th><th>Amended Protocol Text: Version 2.2</th><th>Rationale</th></tr>
<tr><td></td><td>
Table 12: Summary of PK Timepoints for Arm 1
<table>
<tr><th>Sample</th><th>Time-point</th></tr>
<tr><td>1</td><td>Prior to nal-IRI infusion</td></tr>
<tr><td>2</td><td>At the end of the nal-IRI</td></tr>
<tr><td>3</td><td>At the end of the oxalipla</td></tr>
<tr><td>4</td><td>Within 2 hours prior to th</td></tr>
<tr><td>5</td><td>+168 hours/7 days after t</td></tr>
<tr><td>6</td><td>Prior to nal-IRI infusion</td></tr>
<tr><td>7</td><td>End of Treatment visit (3</td></tr>
</table>
*The number of draws corresponds to the number of analytes that will be measured; for example, sample #3 at the end of the oxaliplatin infusion will be used to measure nal-IRI and oxaliplatin.
</td><td>
Table 12: Summary of PK Timepoints for Arm 1
<table>
<tr><th>Sample</th><th>Time-point</th></tr>
<tr><td>1</td><td>Prior to nal-IRI infusion</td></tr>
<tr><td>2</td><td>At the end of the nal-IRI</td></tr>
<tr><td>3</td><td>At the end of the oxalipla</td></tr>
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<tr><td>5</td><td>+168 hours/7 days after t</td></tr>
<tr><td>6</td><td>Prior to nal-IRI infusion</td></tr>
<tr><td>7</td><td>End of Treatment visit (3</td></tr>
</table>
*The number of draws corresponds to the number of analytes that will be measured; for example, sample #3 at the end of the oxaliplatin infusion will be used to measure nal-IRI and oxaliplatin.
7.3.7.2 Arm 2
Patients who are randomized to Arm 2 will undergo collection of blood samples in order to assess the relationship between blood levels of nal-IRI, SN-38 and 5-FU and ECG findings. Directions for collecting, processing and shipping the PK plasma samples can be found in the study manual. PK samples will be collected in Cycle 1 only as outlined in Table 13 below.
</td><td></td></tr>
</table>

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text: Version 2.1</th><th>Amended Protocol Text: Version 2.2</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>Table 13: Summary of PK Timepoints for Arm 2
<table>
<tr><th>Sample</th><th>Time-point</th></tr>
<tr><td>1</td><td>Pre-dose Day 1</td></tr>
<tr><td>2</td><td>After the ECG conducte nal-IRI infusion on Day</td></tr>
<tr><td>3</td><td>After the ECG conducte Day 1</td></tr>
<tr><td>4</td><td>After the ECG conducte 46-hour 5-FU infusion c</td></tr>
<tr><td>5</td><td>After the pre-dose ECG 15</td></tr>
<tr><td>6</td><td>After the ECG conducte infusion on Day 15</td></tr>
<tr><td>7</td><td>After the ECG conducte Day 15</td></tr>
<tr><td>8</td><td>After the ECG conducte FU infusion on Day 15</td></tr>
</table>
*The number of draws corresponds to the number of analytes that will be measured; for example, sample #3 at the 60 minute mark of the 5-FU infusion will be used to measure nal-IRI and 5-FU.</td><td></td></tr>
<tr><td>Section 8.0: Schedule of Assessments</td><td>N/A</td><td>See Table</td><td>The schedule of assessments was updated to reflect the addition of ECG and PK testing to Arm 2, and to add the collection of serum for biomarker analysis.</td></tr>
<tr><td>Section 10.6: Efficacy Analysis</td><td>In the assessments of efficacy, each nal-IRI-containing arm will</td><td>In the assessments of efficacy, each nal-IRI-containing arm will</td><td>The primary endpoint was changed to PFS to enable a more sensitive analysis</td></tr>
</table>

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	be compared to the control arm. Efficacy comparisons will use stratified analyses, incorporating randomization strata. Each comparison will be use 0.10 level one-sided testing to evaluate whether the nal-IRI-containing arm improves the efficacy parameter. Confidence intervals will be presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals will not be adjusted for multiple comparisons. The primary efficacy comparisons will be based on the ITT population, which will included all randomized patients. Tumor evaluation will be measured according to RECIST v1.1. For each patient, progression free survival time will be determined as the time from randomization (for patients in Part 1, the reference start time will be date of first study drug) to the first documented radiographical progression of disease (PD), per investigator using RECIST 1.1, or death from any cause, whichever comes first. If the progression or death occurs at a time point that is	be compared to the control arm. Efficacy comparisons will use stratified analyses, incorporating randomization strata. Each comparison will be use 0.10 level one-sided testing to evaluate whether the nal-IRI-containing arm improves the efficacy parameter. Confidence intervals will be presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals will not be adjusted for multiple comparisons and consequently the experiment-wise type I error may be greater than the 0.10 level. The primary efficacy comparisons will be based on the ITT population, which will included all randomized patients. Tumor evaluation will be measured according to RECIST v1.1. For each patient, progression free survival time will be determined as the time from randomization (for patients in Part 1, the reference start time will be date of first study drug) to the first documented radiographical progression of disease (PD), per investigator using RECIST 1.1, or death from any cause, whichever comes	of the primary endpoint analysis. Assuming a median PFS time of 5.5 months in the control arm and exponential distribution for PFS, an increase in PFS at 24 weeks from 50% to 70% implies a hazard ratio of 0.55. The amendment planned analysis of PFS has 88% power for HR=0.55. Consequently, the endpoint was changed to the more informative standard PFS endpoint.

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	greater than 12 weeks after the non-PD last tumor assessment, then progression-free survival time will be censored at the time of the last non-PD tumor assessment. A primary analysis will be conducted when the Week 24 progression-free status for all randomized patients can be determined, anticipated at approximately 24 weeks after the last patient is randomized. A subsequent analysis for PFS and other endpoints will be performed when PFS events have occurred in at least 120 (i.e. 80% of randomized patients) patients. *Primary Efficacy Analysis* In the intention-to-treat (ITT) analysis, a patient will be considered to have achieved progression-free survival at 24 weeks if the patient has data to indicate the patient has not progressed at 24 weeks. That is, a patient will be considered a responder if there is at least one non-PD assessment, prior to progression or new anticancer therapy, at Week 24 or later. Patients who do not meet the 24-	first. If the progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment, then progression-free survival time will be censored at the time of the last non-PD tumor assessment. Details on censoring rules will be provided in the study statistical analysis plan. A primary analysis will be conducted when there are at least 70 PFS events for each comparison to the control arm. A subsequent analysis for PFS and other endpoints will be performed when PFS events have occurred in at least 120 (i.e. 80% of randomized patients) patients. *Primary Efficacy Analysis* For each arm, PFS will be descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits will be presented. For each nal-IRI-containing arm, PFS will be compared to the control arm. Hypothesis tests will be conducted for differences in PFS using a one-sided stratified log-	

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	week progression-free achievement criteria (e.g. patients progressed/died up to Week 24, patients censored prior to Week 24), If progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment. For each arm, the progression-free survival achievement rate at 24 weeks will be estimated by the number of patients meeting the 24 week achievement criteria divided by the number of ITT patients in the arm. The rate estimates will be presented with corresponding 95% confidence intervals. Each nal-IRI containing arm will be assessed for increase in rate relative to the control arm using a one-sided Cochran-Mantel-Haenszel test, incorporating randomization stratification factors, at 0.10 level of significance. *Secondary Efficacy Analyses* Progression-free Survival (PFS) will be descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits will be presented. For each nal-IRI-	rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models. *Secondary Efficacy Analyses* Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from randomization. Objective Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. Estimates of objective response rate and its corresponding 95% CI will be calculated for each treatment arm. For each nal-IRI-containing arm, ORR will be compared to the control arm.	

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	containing arm, PFS will be compared to the control arm. Hypothesis tests will be conducted for differences in PFS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models. Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from randomization. Objective Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. Estimates of objective response rate and its corresponding 95% CI will be calculated for each	Differences in objective response rate between each nal-IRI-containing arm and control arm will be provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, will be used to compare objective response rates. The maximum reduction (% change from baseline) in CA19-9 will be computed, including analyses by time period (up to Week 8, 16 and 24 visits). CA 19-9 response analyses will be carried out using 3 thresholds for maximum reduction: ≥ 20%, ≥50%, ≥90%. A patient without post-baseline CA19-9 measurement will be considered as a non-responder. Only patients with CA 19-9 elevated (>37 U/mL) at baseline will be included in the analysis of the CA19-9 response. For each threshold and time period, the proportion of CA19-9 response will be estimated, along with corresponding 95% confidence intervals, by treatment arm. Overall Survival (OS) is the time from randomization to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will	

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	treatment arm. For each nal-IRI-containing arm, ORR will be compared to the control arm. Differences in objective response rate between each nal-IRI-containg arm and control arm will be provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, will be used to compare objective response rates. The maximum reduction (% change from baseline) in CA19-9 will be computed, including analyses by time period (up to Week 8, 16 and 24 visits). CA 19-9 response analyses will be carried out using 3 thresholds for maximum reduction: ≥ 20%, ≥50%, ≥90%. A patient without post-baseline CA19-9 measurement will be considered as a non-responder. Only patients with CA 19-9 elevated (>37 U/mL) at baseline will be included in the analysis of the CA19-9 response. For each threshold and time period, the proportion of CA19-9 response will be estimated, along with corresponding 95% confidence intervals, by treatment arm. Overall Survival (OS) is the time from randomization to the date	be censored at the last known alive date. OS will be descriptively summarized for each arm using Kaplan-Meier methodology. For each nal-IRI-containing arm, OS will be compared to the control arm. Hypothesis tests will be conducted for differences in OS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models.	

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	of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. OS will be descriptively summarized for each arm using Kaplan-Meier methodology. For each nal-IRI-containing arm, OS will be compared to the control arm. Hypothesis tests will be conducted for differences in OS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models.		
Section 10.8: Biomarker Subgroup Analysis	Analyses will be performed to assess the associations between potential biomarkers (from plasma and archived tissue) and efficacy parameters (ORR, percent change in target lesion size, and PFS or as appropriate). Graphical displays will be performed when appropriate.	Analyses will be performed to assess the associations between potential biomarkers (from plasma, serum and archived tissue) and efficacy parameters (ORR, percent change in target lesion size, and PFS or as appropriate). Graphical displays will be performed when appropriate.	To clarify that serum samples will also be analyzed.
Section 10.7: Safety Analysis	Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported by the MedDRA version 17.1 or higher. Toxicity will be graded according to the	Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported by the MedDRA version 17.1 or higher. Toxicity will be graded according to the	To address the addition of the QTcF analyses.

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	NCI CTCAE version 4.03. Safety analysis of patients in Part 1 will include a summary of dose-limiting toxicity events. The period for treatment-emergent adverse events and safety findings will be from the time of first study drug administration to 30 days after the date of last study drug administration. If an adverse event begins on the date of first study drug administration with no time recorded, the event will be considered as treatment-emergent. Tabular summaries will be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study drug discontinuation, TEAE-related to study drug and TEAE Grade 3/4. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient. Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data	NCI CTCAE version 4.03. Safety analysis of patients in Part 1 will include a summary of dose-limiting toxicity events. The period for treatment-emergent adverse events and safety findings will be from the time of first study drug administration to 30 days after the date of last study drug administration. If an adverse event begins on the date of first study drug administration with no time recorded, the event will be considered as treatment-emergent. Tabular summaries will be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study drug discontinuation, TEAE-related to study drug and TEAE Grade 3/4. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient. Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data	

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	and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so. Maximum and minimum decrease/increase in continuous laboratory data will be reported. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) will be assessed. Shift to most severe toxicity grade will be summarized. Vital signs and ECG will be tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.	and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so. Maximum and minimum decrease/increase in continuous laboratory data will be reported. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) will be assessed. Shift to most severe toxicity grade will be summarized. Vital signs and ECG will be tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP. Details on the analyses to assess the potential of QTcF prolongation with nal-IRI treatment are provided in Appendix 5.	
Section 10.9: Pharmacokinetics Analysis	10.9: Pharmacokinetics Analysis Plasma concentrations of nal-IRI and oxaliplatin will be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method	10.9: Pharmacokinetics Analysis 10.9.1: Arm 1 Plasma concentrations of total irinotecan, SN-38 and oxaliplatin will be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients will be estimated based	New analysis included to address the addition of pharmacokinetic sampling in Arm 2, and to further characterize the profile of the nal-IRI + 5-FU/LV + oxaliplatin regimen in Arm 1.

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	with priors from the previously estimated (nal-IRI) or published (oxaliplatin) population PK model parameters. The model simulated exposures, e.g., Cmax, AUC (area under the curve), will be used to examine any possible interactions between nal-IRI and oxaliplatin by comparing the least squares geometric mean ratios (LS-GMR) of drug exposures. NONMEM®, Version 7.3, will be used to estimate individual PK parameters and simulate plasma exposures.	on the Empirical Bayesian Estimation method with priors from the previously estimated (nal-IRI) or published (oxaliplatin) population PK model parameters. The model simulated exposures, e.g., Cmax, AUC (area under the curve), will be used to examine any possible interactions between nal-IRI and oxaliplatin by comparing the least squares geometric mean ratios (LS-GMR) of drug exposures. The relationship between dose, PK, and safety endpoints will be evaluated. NONMEM®, Version 7.3, will be used to estimate individual PK parameters and simulate plasma exposures. 10.9.2: Arm 2 Plasma concentrations of total irinotecan, SN-38 and 5-FU will be used to characterize PK parameters. Due to the sparse PK sampling schedule, PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method with priors from the previously estimated population PK models. The model simulated exposures, e.g., Cmax, AUC (area under the	

<table>
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<tr><td></td><td></td><td>curve), will be used to evaluate the relationship between dose, PK, efficacy and safety endpoints. Moreover, the potential for QTcF prolongation will be evaluated from the relationship between PK and QTcF.</td><td></td></tr>
<tr><td>Section 10.10: Sample Size Justification</td><td>The total number of patients enrolled in Part 1 of the study will depend on the number of dose cohorts required to identify the Part 2 dose. Escalation to the next dose cohort will depend on the background toxicity rate (i.e., probability of DLT at a given dose). When 1 of 3 patients develops a DLT and the cohort is expanded to 6 subjects, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of <10%. The table below shows the probability of escalation from cohort to cohort with various toxicity rates.

<table><tr><th>Background Toxicity Rate</th><th>1%</th><th>5%</th></tr><tr><td>Probability of Dose Escalation</td><td>0.999</td><td>0.9</td></tr></table></td><td>The total number of patients enrolled in Part 1 of the study will depend on the number of dose cohorts required to identify the Part 2 dose. Escalation to the next dose cohort will depend on the background toxicity rate (i.e., probability of DLT at a given dose). When 1 of 3 patients develops a DLT and the cohort is expanded to 6 subjects, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of <10%. The table below shows the probability of escalation from cohort to cohort with various toxicity rates.
<table><tr><th>Background Toxicity Rate</th><th>1%</th><th>5%</th></tr><tr><td>Probability of Dose Escalation</td><td>0.999</td><td>0.9</td></tr></table>Part 2 of this study will include a</td><td>The language regarding power calculations was changed to reflect the new primary PFS endpoint in Part 2.</td></tr>
</table>

<table>
<tr><th>Section No. or Title</th><th>Current Protocol Text:
Version 2.1</th><th>Amended Protocol Text:
Version 2.2</th><th>Rationale</th></tr>
<tr><td></td><td>Part 2 of this study will include a comparison of the progression-free survival achievement rate at 24 weeks for each nal-IRI-containing arm versus the control arm.. In the phase 3 MPACT study of nab-paclitaxel plus gemcitabine versus gemcitabine alone, a significant OS advantage was observed with nab-paclitaxel with the median PFS of 5.5 months (compared with 3.7, i.e. 16 weeks, in the gemcitabine alone arm) [2]. The median PFS of 5.5 months corresponds to a PFS rate of 24 weeks of 50%.
The table below illustrates the power to detect differences in PFS achievement rate at 24 weeks between an experimental arm and the control arm using a one-sided comparison at an unadjusted 0.10 level of significance. If the true rate for the control arm is 50%, the study would have 78% power to detect an improvement in an experimental arm that has a true rate of 70%.
<table>
<tr><th>Reference %</th><th>Experimenta</th></tr>
<tr><td>50</td><td>60</td></tr>
<tr><td>50</td><td>65</td></tr>
</table>
</td><td>comparison of the progression-free survival for each nal-IRI-containing arm versus the control arm. In the Phase 3 MPACT study of nab-paclitaxel plus gemcitabine versus gemcitabine alone, a significant OS advantage was observed with nab-paclitaxel with the median PFS of 5.5 months (compared with 3.7 months, i.e. 16 weeks, in the gemcitabine alone arm) [2].
The table below illustrates the power to detect differences in PFS between an experimental arm and the control arm with at least 70 PFS events using a one-sided comparison at an unadjusted 0.10 level of significance. If the true hazard ratio for an experimental arm relative to the control arm is 0.60, the study would have 80% power to detect an improvement with a pairwise one-sided 0.10 level test.
<table>
<tr><th>Hazard ratio for PFS
(experimental vs control)</th><th></th></tr>
<tr><td>0.75</td><td></td></tr>
<tr><td>0.70</td><td></td></tr>
<tr><td>0.65</td><td></td></tr>
<tr><td>0.60</td><td></td></tr>
<tr><td>0.55</td><td></td></tr>
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Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
	50 70 78% 50 71 80% 50 75 91%	50 20 78% 50 21 80% 50 25 91%	
Section 12.7.2: Confidentiality of Biomarker Samples	Blood samples collected as part of the biomarker analysis will be identified only by a number assigned to the patient at the study site; this number will be used in lieu of the patient's name in order to protect the patient's identity. The samples will be stored at a facility designated by the Sponsor. Other than the patient's unique identifying number, no additional patient information that could potentially disclose the patient's identity will be stored with these samples. Samples will be kept until they are used completely for the specified biomarker analyses, or, in the event there is remaining tissue or blood sample available, such specimens will be stored for a maximum of 5 years after approval of the final study report for the clinical trial; at that time, any remaining samples will be destroyed. At the time of informed consent, patients will be able to refuse long-term storage (i.e. 5 years beyond initial specified analyses) of these remaining	Blood samples collected as part of the biomarker analysis will be identified only by a number assigned to the patient at the study site; this number will be used in lieu of the patient's name in order to protect the patient's identity. The samples will be stored at a facility designated by the Sponsor. Other than the patient's unique identifying number, no additional patient information that could potentially disclose the patient's identity will be stored with these samples. Samples will be kept until they are used completely for the specified biomarker analyses, or, in the event there is remaining tissue or blood sample available, such specimens will be stored for a maximum of 5 years after approval of the final study report for the clinical trial; at that time, any remaining samples will be destroyed. Patients may withdraw consent from the study at any time, however, data already collected will not be removed from the study dataset.	To clarify there will not be long term (i.e. 5 years beyond initial specified analyses) or indefinite storage of samples.

Section No. or Title	Current Protocol Text: Version 2.1	Amended Protocol Text: Version 2.2	Rationale
	samples. If long-term storage is refused, any remaining samples will be destroyed following the initial specified analyses. Similarly, patients may withdraw approval at any time by submitting a written request to their study site Investigator. Upon receipt of this withdraw of consent, no further analyses will be completed and the patient's remaining samples will be destroyed, however, data already collected will not be removed from the study dataset. Any samples that a patient consents to be stored indefinitely may be used by the Sponsor for future research. The results from these exploratory analyses may not necessarily be shared with the Investigators or the participating patients.	The results from these exploratory analyses may not necessarily be shared with the Investigators or the participating patients.	
Appendix 4: QTc Substudy Protocol	N/A	Addition of QTc Substudy Protocol	Appendix 4 has been added to detail the instructions for the conduct of the QTc substudy.

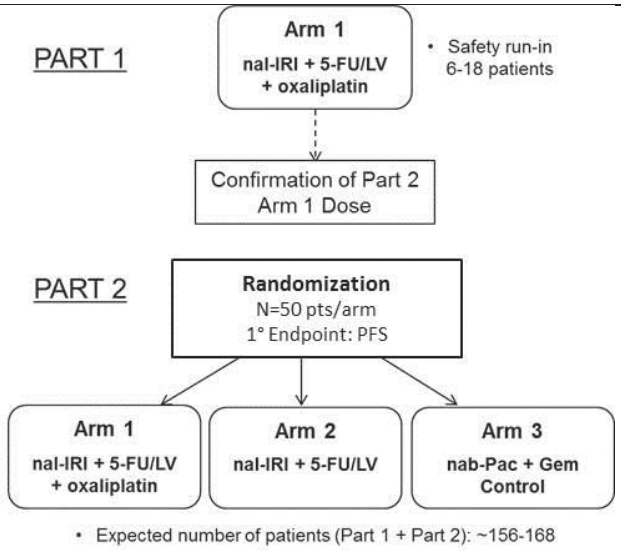
Study Synopsis

This document will serve to detail all changes made to the protocol. Throughout this document deleted text will be indicated with ~~strikethrough~~ and added text will be **bold and underlined**.

Rationale: The synopsis has been updated to reflect all additions and deletions in the main body of the protocol.

Sponsor:	Merrimack Pharmaceuticals
Protocol Title:	A randomized, open-label, Phase 2 study of nanoliposomal irinotecan (nal-IRI)-containing regimens versus nab-paclitaxel plus gemcitabine in patients with previously untreated, metastatic pancreatic adenocarcinoma
Protocol Number:	MM-398-07-02-03
Trial Location:	International; multiple sites
Study Rationale:	Two combination chemotherapy regimens have emerged as standard of care options for first-line treatment of metastatic pancreatic cancer: 5-fluorouricil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX), and nab-paclitaxel + gemcitabine, demonstrating a median overall survival (OS) of 11.1 months and 8.5 months, respectively, in separate Phase 3 studies. Nal-IRI (also known as MM-398) is a nanoliposomal formulation designed to deliver irinotecan to the tumor microenvironment for local drug activation. In a randomized phase 3 study, patients with metastatic pancreatic cancer who had received and progressed on gemcitabine (the NAPOLI-1 study), nal-IRI in combination with 5-FU/LV demonstrated significant clinical activity, increasing OS and PFS relative to 5-FU/LV. The goal of this current study is to assess the preliminary efficacy and safety of nal-IRI-containing regimens, including nal-IRI + 5-FU/LV + oxaliplatin and nal-IRI + 5-FU/LV, in previously untreated metastatic pancreatic cancer patients to assess the most promising regimen for further development.
Primary Objectives:	The study is divided into two parts: Part 1: • To evaluate the safety and tolerability of nal-IRI + 5FU/LV + oxaliplatin • To characterize dose-limiting toxicities (DLTs) associated with nal-IRI + 5FU/LV + oxaliplatin and determine the Part 2 dose of the triplet combination Part 2: • To assess the efficacy of nal-IRI-containing regimens in first-line metastatic pancreatic cancer patients compared to nab-paclitaxel + gemcitabine using ~~the~~ progression-free survival (PFS) ~~rate at 24 weeks~~
Secondary Objectives:	Part 1: • To characterize the pharmacokinetics (PK) of nal-IRI in combination with 5-FU and oxaliplatin Part 2: • To assess efficacy of each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine using overall survival (OS) ~~, PFS,~~ and objective response rate (ORR; CR + PR, per RECIST v1.1)

	• To assess tumor marker CA19-9 response in each nal-IRI-containing regimen relative to nab-paclitaxel + gemcitabine • To assess health-related quality of life (HRQL) using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (EORTC-QLQ-C30) and European Quality of Life Questionnaire (EQ-5D-5L) in each arm • To compare the safety and adverse event profile between the treatment arms • **To assess the potential for QTcF prolongation with nal-IRI treatment**
Exploratory Objectives:	• **To evaluate the relationship between plasma PK of nal-IRI (total irinotecan, SN-38), oxaliplatin, and efficacy and safety endpoints in first-line metastatic pancreatic cancer** • To evaluate blood samples and archived tumor tissue for potential biomarkers that may correlate with nal-IRI PK, toxicity, and/or response nal-IRI
Study Design:	This is an open-label, Phase 2 comparative study to assess the safety, tolerability, and efficacy of nal-IRI in combination with other anticancer therapies, compared to nab-paclitaxel + gemcitabine, in patients with advanced pancreatic adenocarcinoma who have not received prior chemotherapy. This study will assess the following regimens: • nal-IRI + 5-FU/LV + oxaliplatin (Arm 1) • nal-IRI + 5-FU/LV (Arm 2) • nab-paclitaxel + gemcitabine (Arm 3) The study will be conducted in two parts, as illustrated in the schematic below: 1) a safety run-in of the nal-IRI + 5-FU/LV + oxaliplatin regimen, and 2) a randomized, efficacy study of the nal-IRI + 5-FU/LV + oxaliplatin regimen, the nal-IRI + 5-FU/LV combination that previously demonstrated efficacy in the Phase 3 NAPOLI-1 trial (i.e. the NAPOLI regimen), versus a nab-paclitaxel + gemcitabine control arm.



Part 1:

Part 1 will consist of an open-label safety run-in of the combination regimen in Arm 1: nal-IRI + 5-FU/LV + oxaliplatin. The Arm 2 and Arm 3 regimens have established doses, and nal-IRI + 5-FU/LV has been demonstrated tolerable, yielding antitumor responses in a Phase 3 study of patients with relapsed metastatic pancreatic cancer, and therefore will not be included in this part of the study. The safety run-in will enroll small cohorts of patients following a traditional 3 + 3 dose escalation design in order to confirm the target dose of oxaliplatin. Dose limiting toxicities (DLTs) will be evaluated during the first cycle of treatment (i.e. 28 days per cycle; or 14 days after the 2nd dose of study treatment if there is a treatment delay according to Section 7.5) in cohorts of patients to determine if the target combination dose is tolerable (note: the target combination dose is based on the established oxaliplatin dose of the FOLFIRINOX regimen, as published by Conroy *et al.* [1]). If there are no DLTs within the safety evaluation period, then the subsequent cohort will be initiated following agreement between the Investigators, the Medical Monitor, and the Sponsor. If one DLT occurs, then the cohort will be expanded to 6 patients. If 2 or more patients have DLTs within a given dose level, that dose will be considered to exceed the optimal safety and tolerability criteria of the combination, and the dose will not be escalated further; however, lower doses may be explored. The Part 2 dose will then be defined as the next lower dose level in which 6 patients were treated and ≤ 1 patient experienced a DLT.

Since the individual chemotherapies included in the proposed combinations have been studied in previous clinical trials, it is important that the safety assessment takes into account the expected safety profile of the standard dose regimen (e.g. FOLFIRINOX). Any toxicity that is related to disease progression will not be considered a DLT. The following adverse events will be considered as DLTs if they occur during the first cycle of treatment and are deemed related to the study treatment regimen:

	• Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal therapy (withholding study drug and administering concomitant medication, e.g. G-CSF administration for neutropenia) • Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection • Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity • Any grade 4 non-hematologic toxicity with the specific *exclusion* of: o Fatigue/asthenia < 2 weeks in duration o Increases in alkaline phosphatase levels o Nausea and vomiting ≤3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen) o Diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen) The final determination of DLTs will be made following discussion between the DLT review committee (i.e. the Part 1 Investigators, the Medical Monitor, and the Sponsor). As part of this study, pharmacogenomic data will be collected on all patients for determination of UGT1A1*28 status. If a patient in any cohort experiences a DLT, and is found to be homozygous for the UGT1A1*28 allele, the Investigators, Medical Monitor, and Sponsor will assess if the adverse event was attributable to the patient's UGT1A1*28 homozygous status prior to being assigned the category of DLT. Additionally, adverse events meeting the criteria above which are also known adverse reactions of either 5-FU or oxaliplatin based on reported safety data, and unexpected of nal-IRI, will be discussed between the Investigators, Medical Monitor and Sponsor before being assigned the category of DLT in the first cycle of treatment. Following the Cycle 1 safety evaluation period, dose escalation for the next cohort may occur. Patients will continue to be monitored for safety beyond Cycle 1 in order to determine if multiple cycles of treatment are tolerable. Part 2: Part 2 will consist of an open-label, randomized, Phase 2 study in which patients will be randomized to treatment (1:1:1) to either nal-IRI + 5-FU/LV + oxaliplatin, nal-IRI + 5-FU/LV, or gemcitabine + nab-paclitaxel (control regimen). The randomization will be stratified based on region (East Asia vs. rest of the world) and performance status (ECOG 0 vs. 1). **Patients randomized to nal-IRI + 5-FU/LV will undergo serial electrocardiogram recordings and time-matched pharmacokinetic sampling in order to assess any relationship between blood levels of nal-IRI and its metabolite SN-38 and possible QTc interval changes.** An independent Data and Safety Monitoring Board (DSMB) will be utilized to monitor emerging safety data.

	Full details will be listed in a DSMB charter. Translational Research: Translational research components will include collection of blood samples (Parts 1 and 2) and archived tumor (during screening, if available) to look for potential biomarkers. Analyses include cytokine levels (e.g. MCSF1, and IL-6), growth factors (e.g. IGF1 and EGFR family receptors and ligands), or enzyme levels (e.g. MMP9).
Number of Patients:	Approximately 6-18 patients will be enrolled in Part 1. An additional 150 patients (50 patients per arm) will be enrolled during Part 2. Therefore, the total enrollment for the study will be approximately 156-168 patients.
Inclusion Criteria:	a) Pathologically confirmed adenocarcinoma of the pancreas that has not been previously treated in the metastatic setting. • Part 1: unresectable, locally advanced or metastatic disease is allowed, diagnosed within 6 weeks prior to enrollment • Part 2: must have metastatic disease diagnosed within 6 weeks prior to randomization; locally advanced disease is not allowed b) Measurable or non-measurable disease as defined by RECIST v1.1 c) ECOG performance status of 0 or 1 d) Adequate biological parameters as evidenced by the following blood counts: • ANC > 1,500 cells/µl without the use of hematopoietic growth factors, • Platelet count > 100,000 cells/µl, and • Hemoglobin > 9 g/dL e) Adequate hepatic function as evidenced by: • Serum total bilirubin ≤ ULN (biliary drainage is allowed for biliary obstruction), and • AST and ALT ≤ 2.5 x ULN (≤ 5 x ULN is acceptable if liver metastases are present) f) Adequate renal function as evidenced by serum creatinine ≤ 1.5 x ULN, and calculated clearance ≥60 mL/min/~~1.72~~ **1.73** m^2 for patients with serum creatinine levels above or below the institutional normal value. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72); for patients with body mass index (BMI) >30 kg/m^2, lean body weight should be used instead. g) Normal ECG or ECG without any clinically significant findings h) Recovered from the effects of any prior surgery or radiotherapy i) ≥ 18 years of age j) Agreeable to submit unstained archived tumor tissue for analysis, if available k) Able to understand and sign an informed consent (or have a legal representative who is able to do so) l)

Exclusion Criteria:	a) Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy (note: placement of biliary stent is allowed) b) Prior treatment of pancreatic cancer with cytotoxic doses of chemotherapy (patients receiving prior treatment with chemotherapy as a radiation sensitizer are eligible if ≥ 6 months has elapsed from completion of therapy) **c)** ~~Known metastasis to the central nervous system~~ **Uncontrolled CNS metastases (patients who require steroids should be on a stable or decreasing dose)** d) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, diarrhea > grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction e) History of any second malignancy in the last 3 years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 3 years. f) Known hypersensitivity to any of the components of nal-IRI, other liposomal products, or any components of 5-FU, leucovorin or oxaliplatin g) Known hypersensitivity to any of the components of nab-paclitaxel or gemcitabine (Part 2 only) h) Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including: • Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion • NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure • Known historical or active infection with HIV, hepatitis B, or hepatitis C i) 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, patients with tumor fever may be enrolled), which in the investigator's opinion might compromise the patient's participation in the trial or affect the study outcome j) Use of strong CYP3A4 inhibitors or inducers, or presence of any other contraindications for irinotecan[1] k) Presence of any contraindications for 5-FU, leucovorin, or oxaliplatin l) Use of strong CYP2C8 inhibitors or inducers, or presence of any other contraindications for nab-paclitaxel or gemcitabine (Part 2 only)[1] m) Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results

	n) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for **4**~~3~~ months following the last dose of study drug[2]. 1. See Section 7.8 for examples of strong CYP3A4 and CYP2C8 inhibitors or inducers. 2. For a description of highly effective contraceptive measures, please see Appendix 2.
Length of Study:	Patients will be treated until disease progression (radiologic or clinical deterioration), intolerable toxicity, or at the discretion of the treating physician. A follow up clinic visit is required approximately 30 days after last dose of study treatment to complete the final safety assessments. Subsequently, patients will be followed for survival once every 2 months via telephone, email, or clinic visit until death or study closure, whichever occurs first.
Investigational Product:	Nal-IRI (irinotecan liposome injection; also known as MM-398) is irinotecan in the form of the sucrosofate salt, encapsulated in liposomes for intravenous infusion. It will be supplied in sterile, single-use vials containing 10 mL ~~or 9.5 mL~~ of nal-IRI at a concentration of 5 mg/mL. Nal-IRI must be stored refrigerated at 2 to 8°C, with protection from light.
Additional Anti-cancer Therapies:	Depending on the assigned treatment arm, patients may be treated with one or more of the following approved therapies: • 5-FU/LV • oxaliplatin • nab-paclitaxel • gemcitabine Please reference the respective package inserts for additional information.
Dosing Regimens:	All regimens below will be tested in 28-day cycles. Planned cohorts for the Arm 1 safety assessment are described below (Part 1). Dosing will begin at dose level 1, with planned escalation to dose level 2, the target dose of oxaliplatin based on the established FOLFIRINOX regimen [1]. One drug in the triplet combination will be escalated, while the other two drugs are held constant, as indicated in the table below. The dose of nal-IRI and 5-FU/LV in Dose Level 1 and 2 is the same dose and schedule that was previously used in the NAPOLI-1 Phase 3 study. Arm 1: nal-IRI + 5-FU/LV + oxaliplatin • In Part 1, oxaliplatin will be administered at increasing dose levels as indicated in Table 5 (from 60 mg/m2 - 85 mg/m2), IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle • In Part 2, oxaliplatin will be administered at a dose of 85 mg/m2, IV over 120 minutes (±10 minutes), on Days 1 and 15 of each 28-day cycle (if target dose is confirmed in accordance with Section 4.2.3) • nal-IRI 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15

<table>
<tr><td></td><td>of each cycle
• 5-FU 2400 mg/m^2 IV over 46-hours (±60 minutes), on Days 1 and 15 of each cycle
• leucovorin l + d racemic form 400 mg/m^2, IV over 30 minutes (±5 minutes), on Days 1 and 15 of each cycle

Note: The order of infusions on Arm 1 will be as follows: nal-IRI will be administered first, followed by oxaliplatin, then LV, followed by 5-FU. Patients dosed in Part 1 will receive oxaliplatin infusion 2 hours after the completion of the MM-398 infusion (see Section 7.3.1 for details).
<table>
<tr><th>Dose Level*</th><th>Oxaliplatin (mg/m^2)</th><th>5-FU/LV (mg/m^2)</th><th>nal-IRI(mg/m^2)</th></tr>
<tr><td>1</td><td>60
(starting dose)</td><td>2400/400</td><td>80</td></tr>
<tr><td>2**</td><td>85</td><td>2400/400</td><td>80</td></tr>
</table>
*Additional dose levels and dose de-escalation plans are presented in protocol section 5.2
**Dose level 2 is the target dose of oxaliplatin, based on the established FOLFIRINOX regimen published by Conroy *et al.* [1], and will be used in Part 2 of the study following dose confirmation according to Section 4.2.3.

<u>Arm 2: nal-IRI + 5-FU/LV</u>
The dose and regimen that is planned for Arm 2 has been previously studied in 117 patients who participated in the NAPOLI-1 trial, therefore a safety cohort in Part 1 is not needed. The following doses will be administered in Part 2 of the study:
• nal-IRI 80 mg/m^2 IV over 90 minutes (±10 minutes), on Days 1 and 15 of each cycle
• 5-FU 2400 mg/m^2 IV over 46-hours (±60 minutes), on Days 1 and 15 of each cycle
• leucovorin l + d racemic form 400 mg/m^2, IV over 30 minutes (±5 minutes), on Days 1 and 15 of each cycle
<u>Arm 3: nab-paclitaxel + gemcitabine</u>
• nab-paclitaxel 125 mg/m^2 IV over 35 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle
• gemcitabine 1000 mg/m^2 IV over 30 minutes (±5 minutes), on Days 1, 8 and 15 of each 28-day cycle</td></tr>
<tr><td>Criteria for Evaluation:</td><td><u>Part 1:</u> Assessments for safety will include all treated patients and will be based on adverse events, laboratory data, and study treatment related dose-limiting toxicities. Patients who discontinue prior to completion of Cycle 1 due to events that are not related to study treatment toxicity will not be considered in the assessment for DLT, and will be replaced for the purposes of DLT evaluation. Plasma samples will be analyzed for the concentration of nal-IRI (irinotecan) and its metabolites (SN-38 and SN-38G) in order to derive PK parameters of nal-IRI when given in combination with other anticancer therapies. PK parameters of the combination therapies (5-FU and</td></tr>
</table>

	oxaliplatin) will also be analyzed to evaluate any drug interactions with nal-IRI. Part 2: The primary endpoint is progression free survival ~~achievement rate at 24 weeks~~, which will be assessed in all 3 study arms. The secondary endpoints related to efficacy will include overall survival~~, PFS time,~~ and objective response (CR or PR, per RECIST, v 1.1). Achievement of a 20%/50%/90% or greater decrease in CA19-9 levels compared to baseline (at 8, 16, and 24 weeks post-treatment and overall) will also be assessed, along with a quality of life assessment (EORTC-QLQ-C30 and EQ-5D-5L). **QTcF prolongation will be assessed in the Arm 2 (nal-IRI+5-FU/LV) in patients with PK and QTcF measurements.** Translational / Exploratory: Archived tumor tissue (if available) and blood samples will be collected and analyzed for biomarkers (Parts 1 and 2). Samples will be used to explore potential markers of sensitivity and resistance to irinotecan, including, but not limited to, the following: DNA damage repair pathways (e.g. Topo1, BRCA1/2, and SLFN11), growth factor pathways (IGF1 and EGFR family receptors and ligands), and factors involved in CPT-11 conversion to SN-38 (e.g. macrophage content and CES activity).
Statistical Analyses:	The safety population will include all patients receiving any part of at least one dose of study drug. Efficacy and safety analyses will be presented separately for Part 1 and Part 2 of the study. Efficacy comparisons to the control arm, i.e. nab-paclitaxel + gemcitabine, will include only patients enrolled in Part 2. Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum). Tumor evaluation will be measured according to RECIST v1.1. For each patient, progression free survival time will be determined as the time from randomization (for part 1 patients, the reference time will be date of first study drug) to the first documented radiographical progression of disease (PD), per investigator using RECIST 1.1, or death from any cause, whichever comes first. If the progression or death occurs at a time point that is greater than 12 weeks after the non-PD last tumor assessment, then progression-free survival time will be censored at the time of the last non-PD tumor assessment. In the assessments of efficacy, each nal-IRI-containing arm will be compared to the control arm. Efficacy comparisons will use stratified analyses, incorporating randomization strata. Each comparison will use 0.10 level one-sided testing to evaluate whether the nal-IRI-containing arm improves the efficacy parameter. Confidence intervals will be presented at two-sided 95% level for descriptive purposes. Hypothesis tests and confidence intervals will not be adjusted for multiple comparisons **and consequently the experiment-**

	wise type I error rate may exceed the 0.10 level. The primary efficacy comparisons will be based on the ITT population, which will included all randomized patients. A primary analysis will be conducted when the**re are at least 70 PFS events for each comparison to the control arm.** ~~Week 24 progression-free status for all randomized patients can be determined, anticipated at approximately 24 weeks after the last patient is randomized.~~ A subsequent analysis for PFS and other endpoints will be performed when PFS events have occurred in at least 120 patients (i.e. 80% of randomized patients). **Primary Efficacy Analysis** ~~In the intention-to-treat (ITT) analysis, a patient will be considered to have achieved progression-free survival at 24 weeks if the patient has data to indicate the patient has not progressed at 24 weeks. That is, a patient will be considered a responder if there is at lease one non-PD assessment, prior to progression or new anticancer therapy, at Week 24 or later.~~ For each arm, ~~the progression-free survival achievement rate at 24 weeks will be estimated by the number of patients meeting the 24 week achievement criteria divided by the number of ITT patients in the arm. The rate estimates will be presented with corresponding 95% confidence intervals. Each nal-IRI containing arm will be assessed for increase in rate relative to the control arm using a one-sided Cochran-Mantel-Haenszel test, incorporating randomization stratification factors, at 0.10 level of significance.~~ **PFS will be descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits will be presented. For each nal-IRI-containing arm, PFS will be compared to the control arm. Hypothesis tests will be conducted for differences in PFS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models.** **Secondary Efficacy Analyses** ~~Progression-free survival (PFS) will be descriptively summarized for each arm using Kaplan-Meier methodology. Median PFS time and corresponding 95% confidence limits will be presented. For each nal-IRI-containing arm, PFS will be compared to the control arm. Hypothesis tests will be conducted for differences in PFS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models.~~ Best Overall Response (BOR) is defined as the best response as recorded from the start of study drug until disease progression. Patients without a post-baseline tumor assessment will be considered to be non-evaluable for BOR. To classify BOR as stable disease (SD), there should be a qualifying SD assessment at least 6 weeks from randomization. Objective Response Rate (ORR) is defined as the proportion of patients with a BOR characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total

	number of evaluable patients. Only patients with measurable disease at baseline will be included in the analysis of the objective response. Estimates of objective response rate and its corresponding 95% CI will be calculated for each treatment arm. For each nal-IRI-containing arm, ORR will be compared to the control arm. Differences in objective response rate between each nal-IRI-containing arm and control arm will be provided with 95% CIs. Cochran-Mantel-Haenszel tests, adjusting by randomization strata, will be used to compare objective response rates. The maximum reduction (% change from baseline) in CA19-9 will be computed, including analyses at timepoints (up to Week 8, 16 and 24 visits) and overall. Summaries of CA19-9 response will be computed based on three thresholds for magnitude of the maximum reduction: ≥20%, ≥50%, ≥ 90%. A patient without post-baseline CA19-9 measurement will be considered as a non-responder. The proportion of CA19-9 response will be estimated, along with corresponding 95% confidence intervals, for each arm. Overall Survival (OS) is the time from randomization to the date of death from any cause. Patients who are alive or lost to follow-up at the time of the analysis will be censored at the last known alive date. OS will be descriptively summarized for each arm using Kaplan-Meier methodology. For each nal-IRI-containing arm, OS will be compared to the control arm. Hypothesis tests will be conducted for differences in OS using a one-sided stratified log-rank test. Hazard ratios (with 95% confidence interval) for PFS will be estimated using stratified Cox models **Quality of Life Analyses** Analyses of quality of life will be carried out on treated patients who provide baseline and at least 1 post-baseline assessment for the assessment (i.e. there will be an EORTC-QLQ-C30 analysis population and an EQ-5D-5L analysis population). EORTC-QLQ-C30 and EQ-5D-5L results will be summarized at each visit by treatment group Subscale scoring will be carried out as described in the EORTC QLQ-C30 Scoring Manual (Fayers, Aaronson, Bjordal, Curran, & Groenvald, 2001). Linear transformations will be applied to the raw scores so that the reported score will have range 0 100 for all scales. Summary statistics will be presented for each subscale. A summary health state index value will be computed for each EQ-5D-5L assessment. Summary statistics will be presented for summary health state index. For each EQ-5D-5L attribute (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), responses will be tabulated. **Safety Analyses** Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be reported by the MedDRA version 17.1 or higher. Toxicity will be graded according to the NCI CTCAE

	version 4.03. Safety analysis of patients in Part 1 will include a summary of dose-limiting toxicity events. The period for treatment-emergent adverse events and safety findings will be from the time of first study drug administration to 30 days after the date of last study drug administration. If an adverse event begins on the date of first study drug administration with no time recorded, the event will be considered as treatment-emergent. Tabular summaries will be presented for all adverse events, pre-treatment adverse events, treatment-emergent adverse events (TEAE), serious adverse events, adverse events leading to study drug discontinuation, TEAE-related to study drug and TEAE Grade 3/4. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient. Laboratory data will be presented by cycle. Abnormal laboratory values will be assessed using all available data and toxicity grading will be assigned according to NCI CTCAE toxicity scale, where criteria are available to do so. Laboratory, vital signs, and ECG data will be summarized according to parameter type. **Pharmacokinetic Analyses** **Arm 1** Plasma concentrations of ~~nal-IRI~~ **total irinotecan, SN-38, and oxaliplatin** in the combination therapies will be used to characterize PK parameters. PK parameters for individual patients will be estimated based on the Empirical Bayesian Estimation method with priors from the previously published parameters. The model simulated exposures, e.g., C_{max}, AUC (area under the curve), will be compared in order to examine any possible interactions between nal-IRI and the combination therapies **and to evaluate the relationship between dose, PK and safety endpoints**. **Arm 2** **Plasma concentrations of total irinotecan, SN-38 and 5-FU will be characterized based on the Empirical Bayesian Estimation method with priors from previously published parameters. The relationship between dose, PK, efficacy and safety endpoints will be evaluated. Moreover, the relationship between PK and QTcF will be used to evaluate the potential for QTcF prolongation (see below).** **QTcF Analyses** **The potential of QTcF prolongation with nal-IRI treatment will be evaluated in patients in Arm 2, Part 2 of this study. For the primary QTcF prolongation analysis, the predicted changes in QTcF will be obtained from the exposure-QTcF relationship using mixed-effect**

<table>
<tr><td></td><td><u>modeling. Sensitivity analyses will be conducted by evaluating by-timepoint and categorical analyses.</u></td></tr>
<tr><td>Sample Size Justification:</td><td>
The total number of patients enrolled in Part 1 of the study will depend on the number of dose cohorts required to confirm the optimal dose. Escalation to the next dose cohort will depend on the background toxicity rate (i.e., probability of DLT at a given dose). When 1 of 3 patients develops a DLT and the cohort is expanded to 6 subjects, the proposed plan for dose escalation provides a 91% probability that dose escalation will proceed at doses associated with DLT probability of <10%. The table below shows the probability of escalation from cohort to cohort with various toxicity rates.
<table>
<tr><th>Background Toxicity Rate</th><th>1%</th><th>5%</th><th>10%</th><th>20%</th><th>30%</th><th>40%</th><th>50%</th></tr>
<tr><td>Probability of Dose Escalation</td><td>0.999</td><td>0.973</td><td>0.906</td><td>0.709</td><td>0.494</td><td>0.309</td><td>0.172</td></tr>
</table>
Part 2 of this study will include a comparison of the progression-free survival ~~achievement rate at 24 weeks~~ for each nal-IRI-containing arm versus the control arm. In the phase 3 MPACT study of nab-paclitaxel plus gemcitabine versus gemcitabine alone, a significant OS advantage was observed with nab-paclitaxel with the median PFS of 5.5 months (compared with 3.7 months, i.e. 16 weeks, in the gemcitabine alone arm) [2]. ~~The median PFS of 5.5 months corresponds to a PFS rate at 24 weeks of approximately 50%.~~

The table below illustrates the power to detect differences in PFS ~~achievement rate at 24 weeks~~ between an experimental arm and the control arm <u>with at least 70 PFS events</u> using a one-sided comparison at an unadjusted 0.10 level of significance. If the true <u>hazard ratio</u> ~~rate~~ for <u>an experimental arm relative to</u> the control arm is ~~50%~~<u>0.60</u>, the study would have ~~70%~~<u>80%</u> power to detect an improvement <u>with a pairwise one-sided 0.10 level test.</u> ~~in an experimental arm that has a true rate of 70%.~~
<table>
<tr><th>Hazard ratio (experimental vs control)</th><th>Power (≥ 70 events between 2 arms for comparison)</th></tr>
<tr><td>0.75</td><td>47%</td></tr>
<tr><td>0.70</td><td>58%</td></tr>
<tr><td>0.65</td><td>70%</td></tr>
<tr><td>0.60</td><td>80%</td></tr>
<tr><td>0.55</td><td>88%</td></tr>
</table>
<table>
<tr><td>~~Reference %~~</td><td>~~Experimental %~~</td><td>~~Delta % pts~~</td><td>~~Power N=50/arm~~</td></tr>
</table>
</td></tr>
</table>

		~~50~~	~~60~~	~~10~~	~~39%~~	
		~~50~~	~~65~~	~~15~~	~~59%~~	
		~~50~~	~~70~~	~~20~~	~~78%~~	
		~~50~~	~~71~~	~~21~~	~~80%~~	
		50	75	25	91%	

CCI [redacted]

Federal Agency for Medicines and Health Products (FAMHP)
Division Research and Development
Eurostation Building, 8th floor
Victor Horta Place 40 box 40
1060 Brussels
Belgium

13-Feb-2017

EudraCT no.:	2015-003086-28
CCI [redacted]	
Protocol code:	MM-398-07-02-03
Protocol title:	A Randomized, Open-label Phase 2 Study of Nanoliposomal Irinotecan (nal-IRI)-containing Regimens versus nab-Paclitaxel plus Gemcitabine in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma
Sponsor:	Merrimack Pharmaceuticals Inc., Cambridge, MA, USA
EU legal representative	Merrimack Pharmaceuticals U.K. Limited, London, UK
Subject:	**Notification of a Substantial Amendment to Clinical Trial: Clinical Trial Protocol Amendment No. 2, Protocol version 3.1 dated 28 December 2016, Investigator's Brochure version 9.0 dated 15 December 2016.**

Dear Madam/Sir,

On behalf of the Sponsor, Merrimack Pharmaceuticals U.K. Limited, CCI [redacted] herewith would like to notify a Substantial Amendment to the above referenced clinical trial for your review and authorization which comprises the following:

- Clinical Trial Protocol Amendment No. 2, the new protocol version: 3.1 dated 28 December 2016;
- Investigator's Brochure version 9.0 dated 15 December 2016.

The details of this substantial amendment are provided in the enclosed substantial amendment notification form.

Protocol Amendment No. 2:

The sponsor has released a new version of the Clinical Trial Protocol, version 3.1 dated 28 December 2016. The study protocol has been amended to address the identification of the dose level of the study drug for Arm 1 in Part 2 of the study and consequently the dose modification tables. Additionally, in order to align with the most stringent comparator drug Prescribing Information, study exclusion criteria n) has been updated from 4 to 6 months of birth control following last dose of study drug. Finally Section 6.8 Prohibited Therapies has been updated to prohibit subjects from receiving any live attenuated vaccines while participating in the study.

In addition to these three main protocol changes mentioned above, several administrative and editorial changes have been made for clarity, conciseness, accuracy, and consistency of the document.

Rationale for introduced changes and the revised protocol sections are included in the document entitled "MM-398-07-02-03 Version 2 to 3.1: Summary of Changes" enclosed with this submission. In addition, a version in tracked changes mode is provided showing all updates in detail.

The EudraCT application form has been updated in line with this substantial amendment notification. The following sections have been revised:
- A.4.2 and A.4.3 – update of the protocol version and date,
- D.3.6 – the dose of MM-398 has been updated,
- E.3 – update of inclusion criteria,
- E.4 – update of exclusion criteria.

In addition, section G.3 has been revised in order to reflect central facilities that will be used in this clinical trial.

Investigator's Brochure version 9.0 dated 15 December 2016

Merrimack Pharmaceuticals, Inc. has published a new version of the Investigator's Brochure for MM-398. The following substantive changes were implemented:

- Text not relevant to the current stage of the product development was eliminated (streamlined)
- The name of the product was generalized to 'irinotecan liposome injection'
- Introductory information was added for completeness
- Enrollment status in clinical studies and exposure information was updated (as of 20 September 2016)
- The Summary of Guidance for the Investigator was updated to reflect product labeling
- The section describing clinical studies (Effects in Humans) was reorganized to improve clarity
- New content to describe ongoing clinical studies was added as necessary
- A description of a named patient program was added
- Marketing experience was updated to reflect the current development status of the
- product.
- Reference safety information (table of adverse drug reactions) was added.

CCI

The changes made to the previous version of the IB do not affect the risk/benefit ratio of the product. However, there are changes to the reference safety information for assessing whether an adverse reaction is a SUSAR

All introduced changes are reflected in the Investigator's Brochure Summary of Changes.
Ensuing from this amendment (the revision of the study protocol and Investigator's Brochure) the Subject Information Leaflets /Informed Consent Form was updated. [Updated Main Informed Consent Form PART 2 version 2.0, 4 January 2017 (Dutch + French)]

CCI

Documentation
In support of this submission please find enclosed a CDROM containing the XML file of the EudraCT application form and the electronic versions (PDF format) of all documents listed in the attachments.

We trust this notification fulfils your requirements, however, in the event of any queries, please do not hesitate to contact us.

Yours faithfully,

PPD

CCI [redacted]

Early Product Development Project File Note

FILE NOTE	
Sponsor: Ipsen Bioscience, Inc.	CCI [redacted]
Sponsor Study Number: **MM-398-07-02-03**	
Date of Event: N/A	PPD
Site information: (site number/address/contact details if applicable): N/A	

To be completed by Reporter

Clarification / Event Description:	
Protocol Amendment v4.0 dated 03Apr 2017 was never released to sites due pending Sponsor transition from Merrimack to Ipsen at the time. Sites only ever received protocol Version 3.1 dated 20161228 and then the next protocol version distributed by Ipsen to sites was v5.0 dated 20170929. Sites did not submit protocol Version 4.0 to any IRB or submit any associated ICFs.	
Rationale for note to file:	
n/a	
Additional Information (if applicable):	
n/a	
Print Name of Sponsor Representative: PPD	
Signature of Sponsor Representative: e-signed	**Date: e-signed**

The electronic signatures at the end of the document will serve as authentication by the author of this file note.

CCI [redacted]