# A phase II study to evaluate the efficacy of liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-fluorouracil for patients with locally advanced pancreatic carcinoma: Big Ten Cancer Research Consortium BTCRC-GI15-067

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**12AUG2022 (current)**

## PROTOCOL SIGNATURE PAGE

A phase II study to evaluate the efficacy of liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-fluorouracil for patients with locally advanced pancreatic carcinoma:
Big Ten Cancer Research Consortium BTCRC-GI15-067

**VERSION DATE: 12AUG2022**

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

_____ _____
Signature of Site Investigator Date

_____
Site Investigator Name (printed)

_____
Site Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

**PLEASE EMAIL COMPLETED FORM TO**
**BIG TEN CRC ADMINISTRATIVE HEADQUARTERS**

## SYNOPSIS

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|---|---|
| **TITLE** | A phase II study to evaluate the efficacy of liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-fluorouracil for patients with locally advanced pancreatic carcinoma: Big Ten Cancer Research Consortium BTCRC-GI15-067 |
| **PHASE** | II |
| **OBJECTIVES** | Primary Objective:<br>Determine the disease control rate (DCR) of liposomal irinotecan (nal-IRI) in combination with oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) for treatment of locally advanced pancreatic carcinoma.<br><br>Secondary Objectives:<br>1. Describe the objective response rate (ORR) at 8 weeks, 16 weeks, and 24 weeks following starting FOLFOX-nal-IRI.<br>2. Describe the stable disease rate (SDR) at 8 weeks, 16 weeks, and 24 weeks following starting FOLFOX-nal-IRI.<br>3. Describe the proportion of subjects able to undergo surgical resection of tumor.<br>4. Describe the response of serum CA 19-9 after every 2 cycles (every 4 weeks) following starting FOLFOX-nal-IRI.<br>5. Determine progression-free survival (PFS).<br>6. Determine overall survival (OS).<br>7. Describe safety and tolerability of FOLFOX-nal-IRI.<br>8. Describe the quality of life after every 4 cycles (every 8 weeks) following starting FOLFOX-nal-IRI.<br><br>Exploratory Objectives:<br>• Determine FOLFOX-nal-IRI induced DNA damage/repair and apoptosis in biopsied and surgically resected tumor tissues.<br>• Determine DNA damage in blood-based biopsies prior to treatment and following every 4 cycles (8 weeks) of treatment.<br>• Determine the tumor molecular profile prior to initiation of chemotherapy and correlate with treatment responses.<br>• Determine the metabolic profiles of plasma prior to treatment and following every 4 cycles (8 weeks) of treatment.<br>• Examine the inter-institutional variability of the overall resectability rate. |
| **STUDY DESIGN** | This is a phase II, single-arm, open-label, clinical study to investigate the efficacy and tolerability of a combination of liposomal irinotecan (nal-IRI) with oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX-nal-IRI) for treatment of patients with locally advanced pancreatic carcinoma (LAPC). Each subject will be screened for eligibility by evaluation including medical history, physical examination, performance status, blood tests, computed tomographic (CT) scans, and electrocardiogram. Within 28 |

<table>
<tr><td></td><td>days of screening, the consented subjects will have a central venous access device placed and then start treatment.<br>For every 2-week cycle of FOLFOX-nal-IRI, each subject will receive nal-IRI (irinotecan free base 50 mg/m$^2$), oxaliplatin (60 mg/m$^2$), leucovorin (400 mg/m$^2$), and 5-fluorouracil (2,400 mg/m$^2$).<br><br>Tumor response/surgical assessment will be evaluated after every 4 cycles of treatment with CT scans using RECIST 1.1 criteria. If the tumor becomes surgically resectable and the subject is a surgical candidate as determined by a multidisciplinary team, the subject will undergo surgery (at which point he/she would enter survival follow-up). If the tumor remains unresectable and there is no tumor progression, each subject will be treated up to a total of 12 cycles of FOLFOX-nal-IRI.<br><br>Following treatment with 12 cycles of FOLFOX-nal-IRI, if tumor remains unresectable, the subjects may receive further treatment (chemotherapy using the same regimen or of the treating physician’s choice, or chemoradiation therapy) or observation as determined by the physician. During the course of treatment, if the subjects develop unacceptable toxicity and/or disease progression, the treatment will be discontinued, and the subjects will be further managed at the discretion of the treating oncologists.</td></tr>
<tr><td>KEY ELIGIBILITY CRITERIA<br><br>(See Section 3 for complete eligibility details)</td><td>Inclusion Criteria<br>Subject must meet all of the following applicable inclusion criteria to participate in this study:<br>1. Written informed consent and HIPAA authorization for release of personal health information. NOTE: HIPAA authorization may be included in the informed consent or obtained separately.<br>2. Age ≥ 18 years at the time of consent.<br>3. ECOG Performance Status of 0-1 within 28 days prior to registration.<br>4. Histological or cytological confirmation of pancreatic carcinoma.<br>5. Measurable disease according to RECIST v1.1 within 28 days prior to registration.<br>6. Previously untreated pancreatic carcinoma considered as locally advanced unresectable according to NCCN guidelines<br>7. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 14 days prior to initiation of study treatment.<br><br>
<table>
<tr><th>System</th><th>Laboratory Value</th></tr>
<tr><td colspan="2">Hematological</td></tr>
<tr><td>Absolute Neutrophil Count (ANC)</td><td>≥ 1,500 /μL</td></tr>
<tr><td>Hemoglobin (Hgb)</td><td>≥ 8 g/dL; transfusion permitted</td></tr>
<tr><td>Platelet (Plt)</td><td>≥ 100,000 /μL</td></tr>
<tr><td colspan="2">Renal</td></tr>
<tr><td>Serum creatinine<br>OR</td><td>≤ 1.5 × upper limit of normal (ULN)<br>OR</td></tr>
</table>
</td></tr>
</table>

| | |
|---|---|
| Calculated creatinine clearance | ≥ 50 mL/min for subject with creatinine levels > 1.5 ULN |
| **Hepatic** | |
| Total bilirubin | ≤1.5 × ULN (biliary drainage is allowed for biliary obstruction). Patients with Gilbert's syndrome with a total bilirubin ≤3.0 × ULN and direct bilirubin within normal limits are permitted. |
| Aspartate aminotransferase (AST) | ≤ 2.5 × ULN OR<br>≤ 5 x ULN for subjects with liver mets |
| Alanine aminotransferase (ALT) | ≤ 2.5 × ULN OR<br>≤ 5 x ULN for subjects with liver mets |
| **Coagulation** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) | ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as PT, INR, or PTT is within therapeutic range of intended use of anticoagulants |

8. Females of childbearing potential must have a negative serum pregnancy test within 7 days of study registration and within 72 hours of Cycle 1 Day 1.

**Exclusion Criteria**

Subjects meeting any of the criteria below may not participate in the study:

1. Known hypersensitivity to irinotecan liposome, other liposomal products, oxaliplatin, 5-fluorouracil, leucovorin, or any ingredients in those preparations.
2. Pre-existing peripheral neuropathy (Grade 3 or 4) during screening.
3. Major surgery within 4 weeks of starting treatment.
4. Active uncontrolled cardiac arrhythmia or congestive heart failure (class 3 or 4 as defined by the New York Heart Association Functional Classification); or history of myocardial infarction, unstable angina; or acute coronary syndrome within 6 months prior to enrollment.
5. Known history of human immunodeficiency virus (HIV), or hepatic cirrhosis caused by active infection with hepatitis B virus (HBV, as defined by HBsAg positivity or positive DNA). Testing is not required for study entry if there is no clinical suspicion.
6. Any medical condition, life-threatening illness, or organ dysfunction, which in the investigator's opinion, can compromise the subject's safety or put the study outcomes at unnecessary risk.
7. Uncontrolled active systemic infection.
8. Concomitant medications that are prohibited in this study and they cannot be switched to alternative medications.
9. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

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| | 10. Known additional malignancy that is active and/or progressive requiring treatment within 2 years of screening for this study; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, low-grade prostate cancer, or other cancer for which the subject has been disease-free for at least five years. Additional exceptions could be considered if agreed by investigator and principal investigator assuming the disease is considered extremely unlikely to confound evaluation of disease status.<br>11. Treatment with any investigational drug within 30 days prior to registration. |
| **STATISTICAL CONSIDERATIONS** | **Statistical Analysis and Sample Size Justification:**<br>The primary endpoint for this study is disease control rate (DCR).<br><br>In Loehrer *et al*. (J Clin Oncol 2011; 29: 4105-4112) 37 patients with LAPC treated with gemcitabine alone reported an objective response rate (ORR) of 5% and stable disease rate (SDR) of 35%, hence a DCR of 40%. In Lakatos *et al*. (Pathol Oncol Res 2017, 23: 753-759), 32 patients with LAPC were treated with a modified FOLFIRNOX protocol reported an ORR (partial regression only) of 18.8% and SDR of 56.2%, hence a DCR of 75%.<br><br>It is assumed that LAPC patients have a DCR of 45% with standard of care, whereas LAPC patients will have DCR rate of 75% under the protocol in this study. A minimax Simon's two-stage design will be implemented with 12 patients evaluated in the first stage. If 5 or fewer responses are observed from these 12 patients, then the study will be stopped for futility. Otherwise, an additional 13 patients will be added yielding a total sample size of 25 patients. The study will be considered successful if 16 or more responses are observed in the 25 patients. This design comprises a type 1 error rate of 5% and a power of 80% when the true DCR is 75%.<br><br>Therefore, this study seeks to recruit 12 to 25 patients depending on results of the first stage evaluation. Assuming approximately 10% of the patients would not be evaluable, the target sample size is 28 patients. |
| **TOTAL NUMBER OF SUBJECTS** | N = 28 |
| **ESTIMATED ENROLLMENT PERIOD** | 18 months |
| **ESTIMATED STUDY DURATION** | 30 months |

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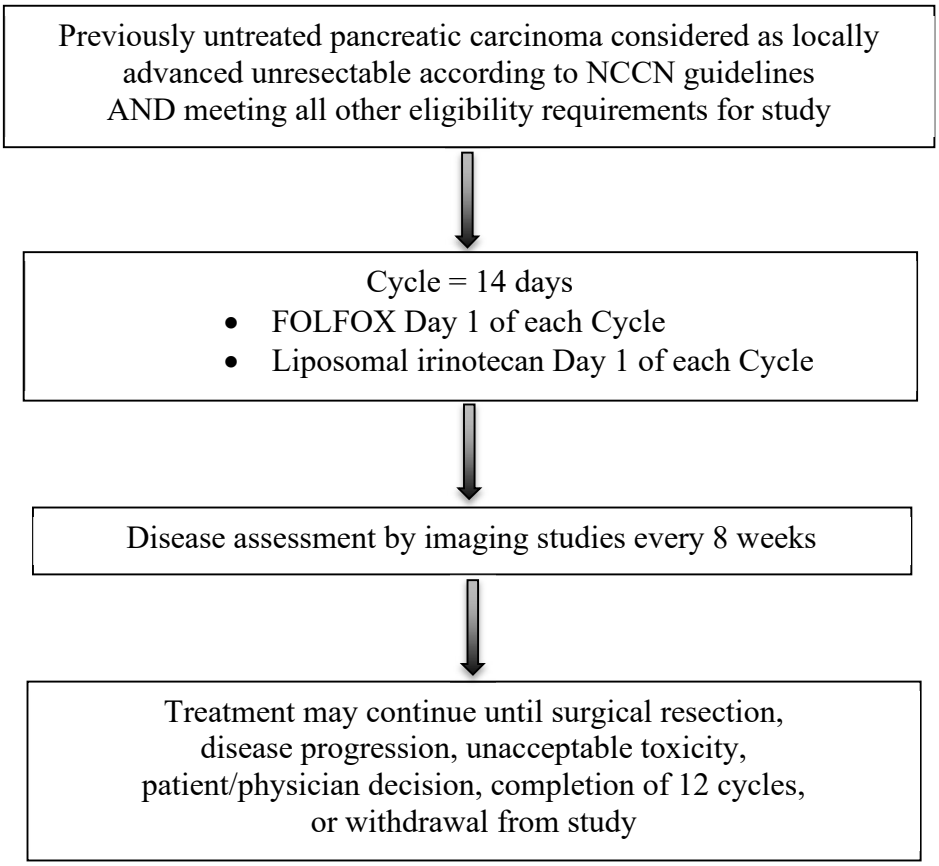
## TREATMENT SCHEMA

A phase II study to evaluate the efficacy of liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-fluorouracil for patients with locally advanced pancreatic carcinoma: Big Ten Cancer Research Consortium BTCRC-GI15-067



# 1. BACKGROUND AND RATIONALE

## 1.1 Background

Adenocarcinoma of the pancreas, which constitutes more than 80% of exocrine pancreatic cancer, has a dismal prognosis. It is the fourth leading cause of cancer-related death in the United States and Europe [American Cancer Society 2018; Malvezzi et al, 2013]. Most patients have advanced or metastatic disease at the time of diagnosis. Although patients are routinely treated with chemotherapy, pancreatic cancer that is not resectable continues to be a highly chemotherapy-resistant, lethal disease with poor prognosis. Patients with advanced or metastatic disease have a 5-year survival rate of only 2%, while the 1-year survival rate for all stages is 27% [Siegel et al, 2018]. While early detection of the disease when it is localized and amenable to surgical resection is important, improved systemic treatment for disease control is urgently needed.

Pancreatic carcinoma is considered locally advanced and unresectable due to vascular involvement as defined by the National Comprehensive Cancer Network (NCCN) Guideline (Version 1.2018). The criteria defining resectability depend on the location of the tumor in the pancreas and its involvement of its surrounding arteries and veins and they are described as follows: Carcinoma located in the head or uncinated process of pancreas are considered unresectable if (i) tumor encases (>180$^{o}$ involvement) of superior mesenteric artery (SMA) or celiac axis (CA); (ii) superior mesenteric vein (SMV) or portal vein (PV) becomes unreconstructible due to tumor involvement or occlusion (caused by either tumor or bland thrombus); (iii) tumor is in contact with the most proximal draining jejunal branch into SMV. On the other hand, carcinoma located in the body or tail of pancreas are considered unresectable if (i) tumor encases (>180$^{o}$ involvement) of superior mesenteric artery (SMA) or celiac axis (CA); (ii) tumor is in contact with CA and aorta; (iii) superior mesenteric vein (SMV) or portal vein (PV) becomes unreconstructible due to tumor involvement or occlusion (caused by either tumor or bland thrombus).

For patients with locally advanced pancreatic carcinoma (LAPC), treatment is generally palliative unless the tumor is down-staged and become resectable in rare instances. For the majority of patients with LAPC, the tumor remains unresectable and the prognosis is poor, with a median survival of 6 to 12 months.

## 1.2 Current Standard of Care

For patients with LAPC, initial treatment typically involves systemic chemotherapy for 6 months, possibly followed by chemoradiation therapy for patients whose tumors have not progressed outside the pancreas. If there is significant down-sizing of tumors (and clearing of vascular involvement in particular), patients may undergo surgical resection of tumor; alternatively, if tumor remains unresectable and without tumor progression, they may receive further chemotherapy or undergo observation.

There is no clearly accepted standard first-line chemotherapy for treatment of LAPC. The chemotherapeutic agents for patients with LAPC are typically based on what being used for palliative treatment of metastatic pancreatic adenocarcinoma. The commonly used drugs include 5-fluorouracil/leucovorin/oxaliplatin/irinotecan (FOLFIRINOX), nab-paclitaxel/gemcitabine, or

gemcitabine [Balaban et al. 2016]. Several studies have shown that FOLFIRINOX has been used for patients with borderline resectable PC (BRPC) or LAPC with variable efficacy [reviewed by Petrelli et al. 2015 and by Suker et al., 2016]. For patients with BRPC treated with FOLFIRINOX, the resection rate and R0 rate are relatively high, but the majority of LAPC remains unresectable following chemotherapy [Hosein et al. 2012; Liu Mondo et al. 2013; Boone et al, 2013; Ferrone et al, 2015; Blazer et al. 2015]. Moreover, FOLFIRINOX may not be considered for patients with suboptimal performance status, and this chemotherapy is associated with intolerable grade 3 or 4 toxicities that lead to reduction of dosage or discontinuation of treatment. Thus, systemic therapy that improves tumor response and resection rate with tolerable toxicity is urgently needed for patients with LAPC.

## 1.3 Liposomal irinotecan (nal-IRI)

This study aims to investigate the efficacy and safety of a combination of liposomal irinotecan (nal-IRI) with oxaliplatin, leucovorin, and 5-fluorouracil in patients with locally advanced pancreatic carcinoma (LAPC).

Irinotecan is a topoisomerase I inhibitor used as an anti-neoplastic agent and has shown significant activity in a variety of tumor types. Irinotecan Hydrochloride Injection (Campto® or Camptosar®) is approved in Asia, Europe, and North America for the treatment of colorectal, lung, gastric, cervical, ovarian, and breast cancers. However, at high dosages, irinotecan causes severe diarrhea and myelosuppression, which are recognized as dose-limiting toxicities and therefore limits the use of more aggressive irinotecan therapy.

Onivyde® (irinotecan liposome injection) is a liposomal formulation of irinotecan designed to maintain or increase its anti-tumor efficacy. Irinotecan liposome injection employs a novel intra-liposomal drug stabilization technology for encapsulation of irinotecan into long- circulating liposome-based nanoparticles with high drug load and high in vivo stability.

Irinotecan liposome injection was approved as Onivyde® in the United States in October 2015, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. Onivyde® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

### 1.3.1 Physical, Chemical, and Pharmaceuticals Summary

An appropriate chemistry, manufacturing, and controls program has been developed to establish the identity and consistent production of irinotecan liposome injection.

The irinotecan liposome injection drug product liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state, as sucrosofate salt. Irinotecan liposome injection is a complex formulation of irinotecan designed to increase circulation time, delay irinotecan release, and increase tumor accumulation. These properties are controlled for by particle size, particle size distribution and percent encapsulated drug. The liposome rigidity and permeability affect how well the drug substance is retained within the liposome. This property is controlled by the 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC): cholesterol ratio and lipid purity. The

amount of drug substance within each liposome controls the amount of lipid which is delivered along with the drug substance and is controlled by the drug to phospholipid ratio.

Irinotecan liposome injection is supplied as a sterile solution containing 4.3 mg/ml of irinotecan on the free base basis (equivalent to 5.0 mg/ml of irinotecan hydrochloride trihydrate) encapsulated in liposomes. The drug product is a sterile, white to slightly yellow opaque isotonic liposomal dispersion for intravenous infusion. Each vial has a nominal fill volume of 10 mL. Each vial is intended for single use administration only. Prior to administration, irinotecan liposome injection must be diluted in 5% Dextrose Injection or Normal Saline (0.9% Sodium Chloride Injection) to a suitable volume for infusion. The solution for infusion (MM- 398 Injection and its admixtures) must not be frozen. Freezing will disrupt the liposome structure and result in the release of free irinotecan. Please see the clinical protocol for instructions on irinotecan liposome injection storage conditions, shelf life, and product administration.

Irinotecan liposome injection has been tested for compatibility with limited materials, and no compatibility issues have been identified.

The only component of biological origin in irinotecan liposome injection is cholesterol, which is derived from sheep wool. Manufacture of irinotecan liposome injection uses cholesterol exclusively derived from sheep in New Zealand, where BSE/TSE has not been reported. The irinotecan liposome injection cGMP manufacturing process extensively controls for reduction and minimization of bioburden throughout production. The drug product is sterile filtered prior to aseptic filling into vials.

Note that irinotecan liposome injection concentration and dosing may be expressed in different ways in different regions, as described in more detail in the investigator brochure. The investigator brochure presents the irinotecan liposome injection concentration and dosing in the historically accepted format using the salt based concentration/strength unless indicated otherwise. It also describes the current approach to concentration and dosing expressions used in various regions.

### 1.3.2 Non-clinical Summary

In non-clinical studies, mouse and rat xenograft or orthotopic models of human breast, gastric, colon, cervical, brain, pancreatic, and lung cancers were used to evaluate the activity of intravenous (IV) irinotecan liposome injection during research and development. Irinotecan liposome injection yielded improved in vivo tumor efficacy not only compared with equal dosing levels of non-liposomal irinotecan, but also in SN-38 exposure-matched studies, where weekly dosing of irinotecan liposome injection at 10 mg/kg showed higher efficacy than 50 mg/kg of unencapsulated irinotecan. Some of the studies showed that irinotecan liposome injection is as much as ~10 times more active in animal models than free irinotecan. This difference in efficacy was linked to the observation that irinotecan liposome injection prolonged the availability of SN-38, the active metabolite of irinotecan, in the tumor.

After IV administration of irinotecan liposome injection in mice, rats, and dogs, the gastrointestinal tract and hematologic system were identified as key target organs of toxicity consistent with the effects of non-liposomal irinotecan. Dose-dependent reversibility of toxicological effects was observed. There were no significant findings in the safety

pharmacology study in dogs at single doses up to 21 mg/kg (420 mg/m$^2$), in which effects on the cardiovascular and respiratory system were assessed. Central nervous system (CNS) toxicity, which was noted in rat studies after administration of non-liposomal irinotecan at 75 mg/kg, was not observed after liposomal administration even at 190 mg/kg. Toxicologic data for irinotecan liposome injection have not identified further toxicity to that determined for non-liposomal irinotecan. In the 18-week repeat-dose toxicity studies, the irinotecan liposome injection NOAEL for rats and dogs is 30 mg/kg (180 mg/m$^2$) and 9 mg/kg (180 mg/m$^2$), respectively. In dogs, the highest non-severely toxic dose (HNSTD) for irinotecan liposome injection is estimated to be between 9 and 15 mg/kg (180-300 mg/m$^2$).

The results of pharmacokinetic studies in rats and dogs after a single infusion of irinotecan liposome injection indicated a longer elimination half-life and lower clearance for the encapsulated active pharmaceutical ingredient (API), irinotecan, than after infusion of non-liposomal irinotecan. At comparable doses, $C_{max}$ was higher with irinotecan liposome injection, while the volume of distribution was lower. Mean residence time (MRT) was longer for irinotecan liposome injection, and overall exposure was higher. During systemic circulation, liposomal encapsulation rates of >95% were maintained. In general, the tissues of rats that received irinotecan liposome injection contained similar maximum concentrations of the API or its metabolite, but these levels were reached later and remained higher for longer than tissue concentrations measured in animals given non-liposomal irinotecan.

In animal pharmacokinetics studies, once irinotecan was released from irinotecan liposome injection liposomes, the metabolic conversion of irinotecan to SN-38 was very similar to that of unencapsulated irinotecan.

### 1.3.3 Clinical Summary

Clinical studies of irinotecan liposome injection have been conducted in the North America, Europe, South America, Australia and Asia. As of 20 September 2017, irinotecan liposome injection has been evaluated in 10 sponsor clinical studies; 3 are ongoing (Studies MM-398- 01-01-02, MM-398-07-02-03, and 331501). Irinotecan liposome injection has also been evaluated in 7 investigator-sponsored clinical studies, of which 4 are ongoing (NCT03086616 CED, CC#13108, SPOC 2012-001 and NCI-9914). In these studies, evaluations included patients with solid tumors, including cervical cancer, gastric cancer, pancreatic cancer, and colorectal cancer. Disease areas currently being studied include glioma (convection-enhanced local delivery), breast cancer, pancreatic cancer, colorectal cancer, and several pediatric solid tumors, including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, and osteosarcoma.

#### 1.3.3.1 Safety

The safety data for irinotecan liposome injection are described in detail in the investigator brochure. The most common adverse reactions (≥20 %) considered to be related to treatment observed in clinical trials of irinotecan liposome injection in combination with 5-fluorouracil and leucovorin, are: diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common laboratory abnormalities (≥10% Grade 3 or 4) were lymphopenia and neutropenia (ONIVYDE® USPI). The most common serious adverse reactions (≥2%) of irinotecan liposome injection were diarrhea, vomiting, febrile neutropenia, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure and thrombocytopenia

(ONIVYDE® European SPC).

The safety of irinotecan liposome injection, a liposomal formulation of irinotecan, may be indirectly compared with the safety of irinotecan, primarily based on a qualitative comparison of adverse reactions reported in the Camptosar® US label for irinotecan and in the US Product Label for ONIVYDE®. The most common adverse reactions of irinotecan and irinotecan liposome injection are similar and are mainly gastrointestinal events and myelosuppression.

Certain known adverse reactions of irinotecan, including anaphylaxis or anaphylactoid reaction, interstitial lung disease-like pulmonary toxicity, and acute pancreatitis, have not been observed with irinotecan liposome injection to date. This could be due to the limited cumulative patient exposure to date of irinotecan liposome injection, 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 will eventually be associated with irinotecan liposome injection.

#### 1.3.3.1.1 Safety Data from Ongoing MM-398-07-02-03 Study

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 (NCT02551991)

This study is an open-label, phase II study to assess the safety, dose-limiting toxicities (Part 1A only), tolerability, and preliminary efficacy of irinotecan liposome injection in combination with oxaliplatin+5-FU/LV in subjects with metastatic pancreatic adenocarcinoma who have not received prior systemic anti-tumor therapy. The study comprises an initial dose exploration (Part 1A) followed by dose expansion (Part 1B ongoing in the extension phase) of the irinotecan liposome injection+ oxaliplatin+5-FU/LV regimen.

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

Treatment-related TEAEs Grade 3 or higher were reported by 41 of 56 subjects, including 22 subjects from the pooled analysis of 32 subjects treated with irinotecan liposome injection 50 mg/m2+LV 400 mg/m2+5-FU 2400 mg/m2 and oxaliplatin 60 mg/m2. The TEAEs included: neutropenia, n=10; febrile neutropenia, hypokalemia, both n=4; diarrhea, nausea, both n=3; anemia, vomiting, both n=2, with no reported Grade 3 or higher fatigue or peripheral neuropathy.

SAEs were reported by 34 of the 56 treated subjects, including 17 of the 32 subjects in the pooled analysis, with 23 subjects reporting treatment-related SAEs. In the pooled analysis, 10 of the 32 subjects had treatment-related SAEs: nausea, febrile neutropenia, both n=3; diarrhea, vomiting, both n=2; colitis, enterocolitis, stomatitis, anemia, pneumonia, and pyrexia, all n=1. At the data cut-off there were no treatment-related TEAEs leading to death.

There were 19 subjects who reported TEAEs leading to discontinuation (including eight subjects in the pooled analysis), with 39 subjects requiring dose adjustment due to AEs (including 26 subjects in the pooled analysis).

Please refer to the current version of the Investigator's Brochure (IB) for complete safety information regarding this drug.

#### 1.3.3.2 Efficacy

The efficacy data for irinotecan liposome injection are described in detail in the investigator brochure. The efficacy profile of treatment with irinotecan liposome injection, in combination with 5- fluorouracil and leucovorin, in patients with metastatic pancreatic cancer previously treated with gemcitabine is derived primarily from the single phase 3 study (Study Number MM 398- 07-03-01, NAPOLI-1), which was initiated following the promising results of a single-arm, phase 2 study of irinotecan liposome injection as a single-agent in the same patient population (Study PEP0208).

Overall in Study PEP0208, 30/40 (75.0%) patients in the Per Protocol population achieved the 3-month survival primary efficacy endpoint (95% CI: 58.8-87.5%) while being treated with irinotecan liposome injection. In addition, 6-month survival was achieved by 17/40 (42.5%) patients and 12-month survival by 10/40 (25.0%) patients.

The basis for the US marketing authorization application of irinotecan liposome injection, in combination with 5-fluorouracil and leucovorin in patients with metastatic pancreatic cancer previously treated with gemcitabine, was the NAPOLI-1 study. The NAPOLI-1 study tested the clinical efficacy and safety of two potentially new treatment options, irinotecan liposome injection monotherapy and irinotecan liposome injection+5FU/LV combination therapy, in pairwise comparison to an active control arm, consisting of 5-FU and leucovorin.

The baseline characteristics of the patient population in the study were considered representative of a pretreated, metastatic pancreatic cancer population, similar to that found in clinical practice, and were balanced across treatment groups. Of 577 screened, 417 patients were randomized and included in the ITT population.

The combination of irinotecan liposome injection+5-FU/LV achieved a median overall survival (OS) of 6.1 months compared to 4.2 months for the control arm of 5-FU/LV alone. The NAPOLI-1 study demonstrated a clinically relevant and statistically significant (p=0.012) superiority of OS in patients receiving the irinotecan liposome injection+5-FU/LV combination over the 5-FU/LV control arm. Additionally, sensitivity analyses supported this primary OS analysis of the irinotecan liposome injection+5-FU/LV combination. The OS benefit was present (or could not be ruled out) in all pre-specified subgroups.

Among the secondary endpoints, PFS, ORR, TTF and CA 19-9 response rate demonstrated statistically significant superiority for the irinotecan liposome injection+5-FU/LV combination over the 5-FU/LV control arm.

## 1.4 Rationale

Clinical studies have documented the therapeutic benefits of encapsulated liposome anti-cancer drugs such as doxorubicin and vincristine [Duggan et al, 2011; Pathak et al, 2014]. Irinotecan is a member of the camptothecin class of topoisomerase I (TOPO1) inhibitors, whose principal mechanism of action leading to cell death is through DNA damage after replication-fork collisions with transiently trapped drug-TOPO1-DNA cleavage complexes, thus emphasizing the length of drug exposure as an important driver for cytotoxicity of camptothecins [Pommier, 2006; Pommier, 2009]. It has shown significant activity in a variety of tumor types. Promising response rates have been observed in many malignancies such as colorectal, non-small cell lung, and small cell lung cancers. However, at higher dosage, irinotecan causes severe diarrhea and myelosuppression, which are recognized as the dose-limiting toxicities and limit the use of more aggressive irinotecan therapy.

Irinotecan liposome injection is a novel liposomal formulation of irinotecan, designed to maintain or increase its anti-tumor efficacy. Irinotecan liposome injection has also been known as PEP02, MM-398, and nal-IRI. Irinotecan liposome injection has been studied in patients with solid tumors, including cervical cancer, gastric cancer, pancreatic cancer and colorectal cancer. Disease areas currently being studied by Ipsen Biopharmaceuticals include metastatic pancreatic cancer, breast cancer, colorectal cancer and pediatric solid tumors, including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma and osteosarcoma. Disease areas currently being studied in investigator-sponsored clinical studies include pancreatic cancer, glioma (intravenous and convection-enhanced local delivery) and breast cancer.

The Food and Drug Administration (FDA)-approved liposomal irinotecan (nal-IRI) has been shown to increase and prolong intratumoral levels of both irinotecan and its active metabolite SN-38 (Wang-Gillam et al. Lancet 2016; 387: 545-557). These data suggest a therapeutic advantage of nal-IRI over the conventionally used irinotecan. Currently, the combination of nal-IRI with 5-fluorouracil and leucovorin is a second line treatment approved by the FDA for metastatic pancreatic adenocarcinoma that has progressed following treatment using nab-paclitaxel and gemcitabine. Whether nal-IRI in combination with oxaliplatin, 5-fluorouracil, and leucovorin improves tumor response and resection rate for patients with LAPC has not been investigated. This proposed study is aimed to test the hypothesis that combination of nal-IRI with oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX-nal-IRI) is a tolerable systemic therapy that improves tumor response, resection rate, and quality of life for patients with LAPC.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1 Objectives

### 2.1.1 Primary Objective

Estimate the disease control rate (DCR) at 24 weeks for nal-IRI in combination with oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX-nal-IRI), in subjects with locally advanced pancreatic carcinoma (for the subjects whose tumors remain unresectable following 12 cycles of FOLFOX-nal-IRI).

### 2.1.2 Secondary Objectives

- Describe the objective response rate (ORR) at 8 weeks, 16 weeks, and 24 weeks following starting FOLFOX-nal-IRI.
- Describe the stable disease rate (SDR) at 8 weeks, 16 weeks, and 24 weeks following starting FOLFOX-nal-IRI.
- Describe the proportion of subjects able to undergo surgical resection of tumor.
- Describe the response of serum CA 19-9 after every 2 cycles (every 4 weeks) following starting FOLFOX-nal-IRI.
- Determine progression-free survival (PFS).
- Determine overall survival (OS).
- Describe safety and tolerability of (FOLFOX-nal-IRI).
- Describe quality of life after every 4 cycles (every 8 weeks) following starting FOLFOX-nal-IRI.

### 2.1.3 Exploratory Objectives

- Determine FOLFOX-nal-IRI induced DNA damage/repair and apoptosis in biopsied and surgically resected tumor tissues.
- Determine DNA damage in blood-based biopsies prior to treatment and following every 4 cycles (8 weeks) of treatment.
- Determine the tumor molecular profile prior to initiation of chemotherapy and correlate with treatment responses.
- Determine the metabolic profiles of plasma prior to treatment and following every 4 cycles (8 weeks) of treatment.
- Examine the inter-institutional variability of the overall resectability rate.

## 2.2 Endpoints

### 2.2.1 Primary Endpoint

Disease control rate (DCR) as determined by the proportion of subjects with complete response, partial response, or stable disease, as defined by RECIST 1.1, at 24 weeks following initiation of FOLFOX-nal-IRI (for the subjects whose tumors remain unresectable following 12 cycles of FOLFOX-nal-IRI).

### 2.2.2 Secondary Endpoints

- Objective response rate (ORR) as determined by the proportion of subjects with either complete response or partial response, as defined by RECIST 1.1, at 8 weeks, 16 weeks, and 24 weeks following initiation of FOLFOX-nal-IRI.
- Stable disease rate (SDR) as determined by the proportion of subjects with no progression of disease as defined by RECIST 1.1, at 8 weeks, 16 weeks, and 24 weeks following initiation of FOLFOX-nal-IRI.
- Rate of resectability as determined by the proportion of subjects who undergo surgical resection of tumors.
- The serum levels of CA 19-9 prior to initiation of chemotherapy and after every 2 cycles (every 4 weeks) following initiation of FOLFOX-nal-IRI.
- Progression-free survival (PFS) as determined by the time interval from the date of first dose of study drug to first documented disease progression or death from any cause, whichever occurs first, if evaluable.
- Overall survival (OS) as defined as the time interval from the date of the first dose of study drug to date of death from any cause.
- Safety and tolerability of FOLFOX-nal-IRI; Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
- Quality of life as measured at baseline and after every 4 cycles (every 8 weeks) using the European Organization for Research and Treatment of Cancer Quality-of-Life Core Questionnaire (EORTC-QLQ-C30).

### 2.2.3 Exploratory Endpoints

- Effect of FOLFOX-nal-IRI DNA damage and apoptosis, in biopsied and surgically resected tumor tissue specimens (for subjects who undergo surgical resection of tumors), as determined by immunohistochemistry (or ELISA) for DNA damage/repair (phosphorylated histone H2AX, ɣH2AX), DNA double strand damage response (p53 binding protein, 53BP1), apoptosis (activated caspase 8 and caspase 3).
- Effect of treatment-induced DNA damage and apoptosis in peripheral blood lymphocytes (PBLs) before treatment and following every 4 cycles (8 weeks) of treatment, as determined by ɣH2AX and 53BP1, and serum biomarkers for apoptosis.
- Molecular profiling as determined by next-generation sequencing of genomic (exon) DNA (*BRCA1*, *BRCA2*, *TP53*, *CDKN2A*, *KRAS*), and correlation with treatment response based on CT scans and serum CA 19-9.
- Metabolic profiles of plasma before treatment and following every 4 cycles (8 weeks) of treatment, as determined by liquid chromatography/tandem mass spectrometry (by metabolomics core facility).
- The inter-institutional variability of the overall resectability rate as determined by central imaging analysis of tumor involvement of regional vasculature.

# 3. ELIGIBILITY CRITERIA

## 3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of consent.
3. ECOG Performance Status of 0-1 **within 28 days** prior to registration.
4. Histological or cytological confirmation of pancreatic carcinoma.
5. Measurable disease according to RECIST v1.1 **within 28 days** prior to registration.
6. Previously untreated pancreatic carcinoma considered as locally advanced unresectable according to NCCN guidelines.
7. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained **within 14 days** prior to initiation of study treatment.

| System | Laboratory Value |
|---|---|
| **Hematological** | |
| Absolute Neutrophil Count (ANC) | ≥ 1,500 /μL |
| Hemoglobin (Hgb) | ≥ 8 g/dL with blood transfusion permitted |
| Platelet (Plt) | ≥ 100,000 /μL |
| **Renal** | |
| Serum creatinine<br><br>Calculated creatinine clearance using the Cockcroft-Gault formula | ≤ 1.5 × upper limit of normal (ULN)<br>OR<br>≥ 50 mL/min for subjects with creatinine levels > 1.5 ULN |
| **Hepatic** | |
| Total bilirubin | ≤1.5 × ULN (biliary drainage is allowed for biliary obstruction). Patients with Gilbert's syndrome with a total bilirubin ≤3.0 × ULN and direct bilirubin within normal limits are permitted. |
| Aspartate aminotransferase (AST) | ≤ 2.5 × ULN |
| Alanine aminotransferase (ALT) | ≤ 2.5 × ULN |
| Albumin | ≥ 3.0 g/dL |
| **Coagulation** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT)<br>Activated Partial Thromboplastin Time (aPTT) | ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as PT, INR or PTT is within therapeutic range of intended use of anticoagulants |

8. Female subjects of childbearing potential must have a negative serum pregnancy test within 7 days of study registration and within 72 hours of Cycle 1 Day 1. **NOTE:** Female subjects are considered of childbearing potential unless they are surgically sterile (have undergone a

hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

9. Female subjects of childbearing potential and males must be willing to abstain from behaviors that could lead to pregnancy (heterosexual activity, sperm donation, in vitro fertilization, etc.) or to use 2 forms of effective methods of contraception from the time of informed consent until 9 months (females) or 6 months (males) after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.
10. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study. The subject should be able to understand the purpose and risks of the study and provide a signed and dated informed consent form.

### 3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Known hypersensitivity to irinotecan liposome, other liposomal products, oxaliplatin, 5-fluorouracil, leucovorin, or any ingredients in those preparations.
2. Pre-existing peripheral neuropathy (Grade 3 or 4) during screening.
3. Major surgery within 4 weeks of starting treatment.
4. Active uncontrolled cardiac arrhythmia or congestive heart failure (class 3 or 4 as defined by the New York Heart Association Functional Classification); or history of myocardial infarction, unstable angina; or acute coronary syndrome within 6 months prior to enrollment.
5. Known history of human immunodeficiency virus (HIV), or hepatic cirrhosis caused by active infection with hepatitis B virus (HBV, as defined by HBsAg positivity or positive DNA). Testing is not required for study entry if there is no clinical suspicion. Note: hepatic cirrhosis caused by other factors (ex. alcoholic cirrhosis) may be considered on a case-by-case basis if, in the opinion of the treating investigator, the disease is unlikely to compromise the subject's safety or put the study outcomes at unnecessary risk.
6. Any medical condition, life-threatening illness, or organ dysfunction, which in the investigator's opinion, can compromise the subject's safety or put the study outcomes at unnecessary risk.
7. Uncontrolled active systemic infection.
8. Concomitant medications that are prohibited in this study and they cannot be switched to alternative medications.
9. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).
10. Known additional malignancy that is active and/or progressive requiring treatment within 2 years of screening for this study; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, low-grade prostate cancer, or other cancer for which the subject has been disease-free for at least five years. Additional exceptions could be

considered if agreed by sponsor-investigator and site investigator assuming the disease is considered extremely unlikely to confound evaluation of disease status.

11. Treatment with any investigational drug within 30 days prior to registration, or within a time interval less than at least 5 half-lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing of this study.

## 4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten Cancer Research Consortium (Big Ten CRC) Administrative Headquarters'(AHQ) electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy and begin therapy **within 5 business days** of registration.

## 5. TREATMENT PLAN

This is a phase II, single-arm, open-label, clinical study to investigate the efficacy and tolerability of a combination of liposomal irinotecan (nal-IRI) with oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX-nal-IRI) for treatment of patients with locally advanced pancreatic carcinoma (LAPC). Each subject will be screened for eligibility and if eligible will be registered to the study. Within 28 days of screening, the consented subjects will have a central venous access device placed and then start treatment.

Subjects will receive FOLFOX-nal-IRI every 2 weeks as described below. Tumor response/surgical assessment will be evaluated after every 4 cycles of treatment with contrast-enhanced CT scans using RECIST 1.1 criteria. If the tumor becomes surgically resectable and the subject is a surgical candidate as determined by a multidisciplinary team at any point, the subject should be removed from study treatment and undergo surgery (at which point he/she would enter survival follow-up). If the tumor remains unresectable and there is no tumor progression, each subject will be treated up to a total of 12 cycles of FOLFOX-nal-IRI. Oxaliplatin could be discontinued for Grade 3 or 4 neuropathy, and the subject would still be considered on study.

Following treatment with 12 cycles of FOLFOX-nal-IRI (for those patients not offered radiotherapy), if the tumor remains unresectable, the subjects may receive further treatment (chemotherapy using the same regimen or of the treating physician's choice, or chemoradiation therapy) or observation as determined by the treating physician. Regardless of choice at this point, patients should be followed for survival.

### 5.1 Pre-medication and Hydration

Premedication and hydration will be provided as per institutional standards. It should be noted that the regimen is considered moderately emetogenic. A corticosteroid and anti-emetic will be administered at least 30 minutes prior to infusion of nal-IRI and oxaliplatin or as per institutional standards.

## 5.2 FOLFOX-nal-IRI Administration

The combination of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) used within the treatment regimen are part of standard of care drugs and they will be provided as per institutional standards.

| Drug/ Sequence | | Dose[1] | Route[2] | Schedule[3] | Cycle Length |
|---|---|---|---|---|---|
| 1 | Oxaliplatin | 60 mg/m$^2$ | Intravenously (IV) over 2 hours (±15 min) | Day 1 | 14 days |
| 2 | Liposomal Irinotecan (free base) | 50 mg/m$^2$ | IV over 90 minutes (±10 min) **after** completion of oxaliplatin | Day 1 | |
| 3 | Leucovorin | 400 mg/m$^2$ | IV over 30 minutes (±5 min) **after** completion of liposomal Irinotecan | Day 1 | |
| 4 | 5-Fluorouracil | 2,400 mg/m$^2$ | IV over 46 hours via infusion pump at home (±1 hr) | Day 1 | |

[1] Body surface area (BSA) should be recalculated when weight changes by ≥ 10% according to the Mosteller formula.
[2] Drug administration times performed outside the above recommended windows will not be considered as protocol deviations.
[3] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

## 5.3 Concomitant Medications

### 5.3.1 Allowed Concomitant Medications

All treatments the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Transfusion of blood products and administration of myeloid growth factors may be considered for chemotherapy-induced myelosuppression including anemia, thrombocytopenia, and neutropenia as indicated by signs and symptoms, laboratory results, and as determined by the investigator.

All concomitant medications received within 28 days before the first dose of study drug through 30 days after the last dose of study drug should be recorded in the EDC. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded only if associated with a serious adverse event (SAE) as defined in Section 11.1.2 and if the SAE meets the reporting criteria in Section 11.2.2.

Medications administered during a procedure (anesthetics, etc.) will not be collected as concomitant medications. However, the procedure itself should be recorded on the adverse event page of the EDC.

### 5.3.2 Prohibited Concomitant Medications

*Strong CYP3A4 inducers*

Patients receiving concomitant non-liposomal irinotecan and CYP3A4 enzyme-inducing anti-convulsants including phenytoin, phenobarbital or carbamazepine have substantially reduced exposure to irinotecan (AUC reduction by 12% with St John's wort, 57%-79% with phenytoin, phenobarbital, or carbamazepine) and SN-38 (AUC reduction by 42% with St John's wort, 36%-92% with phenytoin phenobarbital, or carbamazepine). Therefore, co-administration of irinotecan liposome injection with inducers of CYP3A4 may reduce systemic exposure of irinotecan liposome injection.

*Strong CYP3A4 inhibitors and UGT1A1 inhibitors*
Patients receiving concomitant non-liposomal irinotecan and ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased SN-38 exposure by 109%. Therefore, co-administration of irinotecan liposome injection with other inhibitors of CYP3A4 (e.g. grapefruit juice, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) may increase systemic exposure of irinotecan liposome injection. Based on the drug interaction of non-liposomal irinotecan and ketoconazole, co-administration of irinotecan liposome injection with other inhibitors of UGT1A1 (e.g. atazanavir, gemfibrozil, indinavir) may also increase systemic exposure of irinotecan liposome injection.

The prohibited medications are listed in Table 1 in the protocol appendix.

## 5.4 Supportive Care

Drugs-associated toxicities may require symptomatic management and may be administered at the discretion of the investigator in keeping with the community standards of medical care. For example, irinotecan liposome injection can cause life-threatening myelosuppression, neutropenia, and diarrhea. The complications of neutropenia such as neutropenic fever and neutropenic sepsis should be managed promptly with antibiotics; granulocyte-colony stimulating factor (G-CSF) may be used to manage neutropenia at the investigator's discretion. Early-onset diarrhea (occurring during or shortly after infusion of irinotecan) may be prevented by pre-medication with atropine prior to administration of irinotecan liposome injection. Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) should be treated promptly with loperamide, fluid and electrolyte replacement for dehydration, and antibiotics if ileus, fever, or severe neutropenia develops. In case of severe hypersensitivity reactions, acute infusion reactions (rash, urticarial, periorbital edema, pruritis), or interstitial lung disease (dyspnea, cough, fever), irinotecan liposome injection should be discontinued, and the symptoms should be managed according to existing standard guidelines.

## 5.5 Reproductive Information

Participants of childbearing potential who are sexually active and their partners must agree to abstain from behaviors that could lead to pregnancy (heterosexual activity, sperm donation, in vitro fertilization, etc.) or to use 2 forms of effective methods of contraception beginning with time of consent, during the study treatment and for 9 months (females) or 6 months (males) after last dose of study treatment(s). Two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method. See below for options of acceptable non-hormonal birth control methods:

- Total sexual abstinence i.e., refrain from any form of sexual intercourse in line with the patients' usual and/or preferred lifestyle. Abstinence must be for the total duration of the

study treatment and for at least 9 months (females) or 6 months (males) after the last dose of study treatment. Periodic abstinence (e.g., calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine Device PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:
- Etonogestrel implants (eg, Implanon®, Norplant®) PLUS male condom
- Normal and low dose combined oral pills PLUS male condom
- Hormonal shot or injection (eg, Depo-Provera) PLUS male condom
- Intrauterine system device (eg, levonorgestrel-releasing intrauterine system - Mirena®) PLUS male condom

# 6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

## 6.1 Dose Delays/Dose Modifications

Unless otherwise noted in the dose modification tables below, treatment may be delayed up to 28 days from the expected day of the next treatment for any reason. If treatment is delayed ≤ 28 days, subjects will proceed with the next cycle of treatment at the dose level recommended according to the tables below. Any dosing interruption will not increase the duration of the cycle or treatment. Held or missed doses will not be made up.

If a treating investigator determines a dose reduction is in a subject's best interest, yet the subject fails to meet the guidelines below, the dose reduction must be discussed with the sponsor investigator on a case-by-case basis. Please contact the Big Ten CRC project manager to arrange this discussion.

## 6.2 Dose Levels for Dose Reductions

If dose level below that outlined in the table is required, subject will be removed from protocol mandated treatment and followed-up per protocol.

| Dose level | Dose of Irinotecan liposome injection (free base) | Dose of Oxaliplatin | Dose of 5-Fluorouracil |
|---|---|---|---|
| **Starting Dose** | 50 mg/m$^2$ | 60 mg/m$^2$ | 2,400 mg/m$^2$ |
| **Dose level (-1)** | 40 mg/m$^2$ | 48 mg/m$^2$ | 1,920 mg/m$^2$ |

| | | | |
|---|---|---|---|
| **Dose level (-2)** | 30 mg/m$^2$ | 36 mg/m$^2$ | 1,440 mg/m$^2$ |

### 6.2.1 Dose Reduction of nal-IRI

a. If the subject develops grade 3 or 4 diarrhea, nal-IRI will be withheld until diarrhea resolves to ≤ grade 1. Loperamide will be initiated for late onset diarrhea of any severity. Intravenous or subcutaneous atropine 0.25 mg to 1 mg will be administered (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to Grade 1, resume nal-IRI at 40 mg/m$^2$ for first occurrence or 30 mg/m$^2$ for second occurrence; discontinue nal-IRI for third occurrence.
b. If the subject develops interstitial lung disease or anaphylactic reaction, nal-IRI will be discontinued at first occurrence.

### 6.2.2 Dose Reduction of Oxaliplatin

a. If the subject develops persistent grade 2 neurosensory events, the dose of oxaliplatin will be reduced to 48 mg/m$^2$ for first occurrence, or 36 mg/m$^2$ for second occurrence.
b. If the subject develops grade 3 or 4 gastrointestinal toxicities (despite prophylactic treatment) and recovers from them, the dose of oxaliplatin will be reduced to 48 mg/m$^2$ for first occurrence, or 36 mg/m$^2$ for second occurrence.
c. If the subject develops grade 4 neutropenia or febrile neutropenia or grade 3/4 thrombocytopenia, the next dose will be delayed until neutrophils 1,500/μL and platelets 75,000//μL. Granulocyte colony-stimulating factor (G-CSF) may be administered as indicated.
d. If the subject develops persistent grade 3 neurosensory events, discontinue oxaliplatin.

### 6.2.3 Dose Reduction of 5-Fluorouracil

a. 5-fluorouracil will be held for any of the following:
   - Grade 3 or 4 diarrhea
   - Grade 2 or 3 palmar-plantar erythrodysesthesia (hand-foot syndrome)
   - Grade 3 or 4 mucositis
   - Grade 4 myelosuppression
b. Upon resolution or improvement to Grade 1 diarrhea, mucositis, myelosuppression, or palmar-plantar erythrodysesthesia, resume administration of 5-fluorouracil at 1,920 mg/m$^2$ for first occurrence, or 1,440 mg/m$^2$ for second occurrence.
c. 5-fluorouracil will be discontinued following development of any of the following adverse reactions:
   - Angina, myocardial infarction/ischemia, arrhythmia, or heart failure in patients with no history of coronary artery disease or myocardial dysfunction
   - Hyperammonemic encephalopathy
   - Acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbance

## 6.3 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed up per protocol under the circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression

- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If protocol therapy is interrupted for ≥ 28 days.

## 6.4 Protocol Discontinuation

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The site study team should contact the subject (ex. telephone, telehealth, clinic visit, etc.) to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF.

## 7. STUDY CALENDAR & EVALUATIONS

| Cycle = 14 days | Screen | Cycle 1 | Cycle 2-12 | Safety follow up[14] | Survival Follow Up[15] |
|---|---|---|---|---|---|
| | -28 days | Day 1 (±3) | Day 1 (±3) | 30 days post Tx | Q 3 months ± 14 days |
| **REQUIRED ASSESSMENTS** | | | | | |
| Informed Consent | X | | | | |
| Medical history[1] | X | | | | |
| Physical exam | X | X | X | X | |
| Vital signs, ECOG Performance status[2] | X | X | X | X | |
| ECG | X | | | | |
| Quality of Life assessment (EORTC-QLQ-C30)[3] | | X[3] | Q 4 cycles[3] | X | |
| AEs & concomitant medications | X | X | X | X | |
| **LABORATORY ASSESSMENTS** | | | | | |
| Complete Blood Cell Count with diff (CBC)[4] | -14d | X[13] | X | X | |
| Comprehensive Metabolic Profile (CMP)[4] | -14d | X[13] | X | X | |
| CA 19-9[5] | X | X[13] | Q 2 cycles[5] | X | |
| PT/INR and aPTT | -14d | | | | |
| Pregnancy test (serum) WOCBP[6] | -7d | -72h | | | |
| **DISEASE ASSESSMENT** | | | | | |
| CT of chest[7] | X | | Q 4 cycles | | |
| CT or MRI of abdomen and pelvis[7] | X | | Q 4 cycles | | |
| MRI Brain[7] | X | | | | |
| Bone/PET Scan[7] | X | | | | |
| **TREATMENT EXPOSURE** | | | | | |
| FOLFOX | | X | X | | |
| Liposomal Irinotecan | | X | X | | |
| **CORRELATIVE STUDIES (SPECIMEN COLLECTION)** | | | | | |
| Prior Genetic Sequencing Results[8] | | X | | | |
| Fresh Biopsy[8] | | | | at resection[8] | |
| Blood samples[9] | | X[9] | Q 2 cycles[9] | X | |
| Central submission of CT/MRI images[16] | | | | X | |
| **BANKING SAMPLES (SPECIMEN COLLECTION)** | | | | | |
| Whole Blood[10] | | X | | | |
| Unstained Slides[11](if available) | | X | | | |
| Serum and Plasma[12] | | X | | X | |
| **FOLLOW UP** | | | | | |
| Survival status, initiation of new anti-cancer therapy | | | | | X |

**Key to Footnotes**

**1**: Medical History (clinically significant medical history as determined by the treating physician); other data to be obtained includes: diagnosis and staging (pathology report and staging documentation [TNM staging]), smoking history questionnaire and trial awareness question, prior anti-cancer treatment including medications, [chemotherapy, checkpoint inhibitors, etc.], radiation and surgery.

**2**: Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status

**3**: Assessment of quality of life: prior to treatment on Cycle 1 Day 1 then after every 4 cycles of FOLFOX-nal-IRI (every 8 weeks) and at the safety follow up visit. If a cycle is delayed, QOL assessment should also be delayed. Assessment will be done using the EORTC-QLQ-C30.

**4**: CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase. CBC with differential and platelet count to include WBC, Hgb, ANC and platelet count.

**5**: CA19-9 will be drawn prior to treatment on Cycle 1 Day 1 then after every 2 cycles of FOLFOX-nal-IRI (that is, every 4 weeks) and at the safety follow up visit. If a cycle is delayed, CA19-9 should also be delayed.

**6**: For women of childbearing potential (WOCBP): serum βhCG, within 7 days prior to study registration. WOCBP must also have a negative serum pregnancy test within 72 hours of Cycle 1 Day 1.

**7**: Tumor response will be performed at screening then after every 4 cycles (every 8 weeks); tumor imaging to be done at treatment discontinuation at discretion of investigator. CT pancreas triple phase with pelvis and chest CT may replace the CT chest-abdomen-pelvis if clinically indicated. Baseline bone scan will be obtained if there is any suspicion of metastatic bone involvement. If bone scan is positive at baseline, subjects will be excluded from the study. A screening MRI of brain should be performed to evaluate for the presence of brain metastases as clinically indicated. A CT scan of the brain may be done if MRI is contraindicated. A ±7-day window will apply to all imaging.

**8**: If prior genetic sequencing results were performed as per standard of care, they will be submitted at C1D1. See also Section 8.1. If the subject undergoes surgical resection, tissue will be required from that procedure. All specimens will be used for biospecimen-based research.

**9**: Research Blood Samples will be collected prior to treatment on Cycle 1 Day 1 then after every 2 cycles (every 4 weeks) starting at Cycle 3 Day 1 of FOLFOX-nal-IRI and at the safety follow up visit. These samples will be used for correlative testing as described in Section 8. See CLM for collection, processing, labeling and shipping instructions.

**10**: Whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling and shipping instructions.

**11**: Submission of unstained slides for banking from an archived FFPE tumor block (if available). See CLM for collection, labeling, and shipping instructions.

**12**: Serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the 30-Day Safety Follow up visit. See CLM for collection, labeling, processing, and shipping instructions.

**13**: If screening (baseline) labs were performed within 7 days of Cycle 1 Day 1 of treatment, these do not need to be repeated.

**14**: When subjects permanently stop study treatment for whatever reason, a safety follow-up visit will occur 30 days (+7 days) after the last dose of treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

**15**: Subjects without documented disease progression will be followed for disease progression every 3 months for 1 year from Day 30 visit. Once disease progression is documented, subjects will enter a survival follow up period every 3 months from the time of documented progression until death or lost to follow up. This follow up may be accomplished via phone call, email, telehealth, or communication with a local physician.

**16**: All CT/MRI images obtained throughout the study will be submitted for central analysis at the end of the study.

### 7.1 Safety Follow-up Evaluations

A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (+7 days) after the last dose of treatment or before the initiation of a new anti-cancer treatment, whichever comes first. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

### 7.2 Long Term Follow-up Evaluations

Subjects without documented disease progression will be followed for disease progression every 3 months for 1 year from day 30 visit. Once disease progression is documented, subjects will enter a survival follow up period every 3 months from the time of documented progression until death or lost to follow up. This follow up may be accomplished via phone call, email, telehealth, or communication with a local physician.

## 8. BIOSPECIMEN STUDIES AND PROCEDURES

### 8.1 Prior Genetic Sequencing Results

If prior genetic sequencing results were performed as per standard of care, they will be submitted at C1D1. If prior genetic sequencing was not performed, it should be ordered as standard of care. In this case, a subject may be enrolled, and genetic sequencing results will be submitted when available. If a subject does not have archival tissue available, a new biopsy is recommended but is not mandatory. In particular, markers such as BRCA1, BRAC2, TP53, CDKN2A, and KRAS will be noted in the database. Results of tumor molecular profiling may be used for correlation with tumor response to treatment.

### 8.2 Tissue from Surgical Resection

For subjects that undergo surgical resection, a sample of this tissue is required. This sample may be analyzed for molecular profiling including expression of biomarkers and somatic mutations by next-generation sequencing. Results of tumor molecular profiling may be used for correlation with tumor response to treatment.

### 8.3 Peripheral Blood

Peripheral blood collection will occur prior to treatment on cycle 1, day 1, then after every 2 cycles of FOLFOX-nal-IRI (that is, every 4 weeks) and at the safety follow up visit. Plasma will be processed from the peripheral blood for future metabolite profiling and circulating tumor DNA analysis.

### 8.4 Central Image Analysis

Central image analysis on coded images will be performed at the end of the study to analyze inter-institutional variability of the overall resectability rate. All CT/MRI images obtained throughout the study will be submitted at the end of study. See Imaging Manual for image labeling and shipping/transfer instructions.

### 8.5 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

### 8.5 Banking Samples for Future Unspecified Research

Subject consent will be obtained to collect additional samples and store coded images for future unspecified Big Ten Cancer Research Consortium studies. HCRN will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.
This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Central image analysis and storage of coded images. These images will be stored centrally at Penn State for future use after the planned analysis for this trial.

Please refer to the Correlative Laboratory Manual (CLM) and Imaging Manual for all sample collection, processing, labeling, and shipping instructions.

### 8.6 Confidentiality of Biospecimens

Samples will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

## 9. CRITERIA FOR DISEASE EVALUATION

### 9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

#### 9.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

### 9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable

disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

**NOTE:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

### 9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

### 9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 9.5 Evaluation of Target Lesions

**NOTE:** In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. |
| Partial Response (PR) | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters |
| Progressive Disease (PD) | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the |

| | |
|---|---|
| | appearance of one or more new lesions is also considered progressions). |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study |

## 9.6 Evaluation of Non-target Lesions

| | |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)<br><br>Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response. |
| Non-CR/ Non-PD | Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits |
| Progressive Disease (PD) | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. |

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

## 9.7 Evaluation of Overall Response

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/ Non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD/ or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | Non-evaluable |
| PD | Any | Yes or No | PD |
| Any | PD* | Yes or No | PD |
| Any | Any | Yes | PD |
| *In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. | | | |

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

## 9.8 Definitions for Response Evaluation – RECIST 1.1

### 9.8.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

### 9.8.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

### 9.8.3 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

### 9.8.4 Disease Control Rate

The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

# 10. DRUG INFORMATION

## 10.1 Liposomal Irinotecan (nal-IRI)

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this drug.

The irinotecan liposome injection drug product contains the drug substance irinotecan in the amount equivalent to 5 mg/mL of irinotecan hydrochloride trihydrate. The drug product liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state, as the sucrosofate salt. The liposome carriers are composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 6.81 mg/mL; cholesterol, 2.22 mg/mL; and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidylethanolamine (MPEG-2000-DSPE), 0.12

mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl] ethanesulfonic acid (HEPES) as a buffer, 4.05 mg/mL; sodium chloride as isotonicity reagent, 8.42 mg/mL; and sucrose octasulfate as the drug trapping agent, 0.9 mg/mL. The solution is buffered at pH 7.25. In the vialed product, greater than 98% of the drug is encapsulated in the liposome carrier. Irinotecan liposome injection is supplied as a sterile solution containing 4.3 mg/ml of irinotecan free base encapsulated in liposomes. The appearance of irinotecan liposome injection is white to slightly yellow opaque liquid.

### 10.1.1 Supplier/How Supplied

Ipsen Biopharmaceuticals will supply Irinotecan liposome injection at no charge to subjects participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

### 10.1.2 Preparation

Irinotecan liposome injection is supplied as a sterile solution containing 4.3 mg/ml of irinotecan on the free base basis (equivalent to 5.0 mg/ml of irinotecan hydrochloride trihydrate) encapsulated in liposomes. Prior to administration, irinotecan liposome injection drug product must be diluted in 5% Dextrose Injection or Normal Saline to a suitable volume for infusion. Irinotecan liposome injection and admixtures of irinotecan liposome injection must not be frozen, as freezing temperature may disrupt the liposome structure in the drug product and lead to the release of free irinotecan.

### 10.1.3 Storage and Stability

Please see the clinical protocol and product labels for instructions on irinotecan liposome injection storage conditions, shelf life, and product administration. Prior to administration, irinotecan liposome injection must be diluted in 5% Dextrose Injection or Normal Saline (0.9% Sodium Chloride Injection) to a suitable volume for infusion. The solution for infusion (irinotecan liposome injection and its admixtures) must not be frozen. Freezing will disrupt the liposome structure and result in the release of free irinotecan. Because of the potential for microbial contamination during dilution, the solution for infusion should be used immediately, but may be stored at room temperature (15º to 30ºC) for up to 4 hours prior to the start of the infusion. If necessary, the solution for infusion may be refrigerated (2º to 8ºC) for no more than 24 hours prior to use. Irinotecan liposome injection has been tested for compatibility with limited materials, and no compatibility issues have been identified. The following materials were tested:

- Infusion sets (without in-line filter) made of PVC or polyethylene lined
- IV bags made of PVC or coextruded film of polyolefin/polyamide

Store Irinotecan liposome injection at 2ºC to 8ºC (36°F to 46°F). Do NOT freeze. Protect from light.

### 10.1.4 Administration

Irinotecan liposome injection should be infused over 90 minutes (±10 min) without the use of in-line filters. Premedication with a corticosteroid and an anti-emetic at least 30 minutes prior to

administration of irinotecan liposome injection is recommended to prevent nausea/vomiting and to decrease the risk of infusion reaction.

#### 10.1.5 Handling and Disposal

Irinotecan liposome injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.

#### 10.1.6 Dispensing

Irinotecan liposome injection must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Irinotecan liposome injection should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

#### 10.1.7 Adverse Events

Please see the current IB for a detailed list of adverse events. Most common related to Irinotecan liposome injection include hair loss, dizziness, hypomagnesemia, hypokalemia, decreased appetite and decreased weight.

### 10.2 FOLFOX

Please refer to the latest version of the prescribing information for each medication. This information can be found at fda.gov and/or on the manufacturer's website. Commercial supplies of each drug will be used in this study and billed to third party payers or the subject. Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

#### 10.2.1 Oxaliplatin

Please refer to the package insert for complete product information.

##### 10.2.1.1 Availability

Oxaliplatin is commercially available as an aqueous solution in vials containing 50 mg and 100 mg at a concentration of 5 mg/mL. The vials do not contain any preservative and they are intended for single use.

##### 10.2.1.2 Storage and Stability

Intact vials should be stored at room temperature. Solutions diluted in D5W are stable for 6 hours at room temperature or 24 hours under refrigeration.

##### 10.2.1.3 Preparation

The calculated dose of oxaliplatin should be diluted for infusion with 250 mL to 500 mL D5W. Oxaliplatin should not be diluted with a sodium chloride solution. Needles, syringes, catheters or IV administration sets containing aluminum should not be used with oxaliplatin. As with other platinum compounds, contact with aluminum may result in a black precipitate.

#### 10.2.1.4 Disposal

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

#### 10.2.1.5 Administration

Oxaliplatin will be administered by intravenous infusion over 2 hours (or per institutional standards). Infusion time may be prolonged (up to 6 hours) in subjects experiencing pharyngolaryngeal dysesthesia.

Oxaliplatin is unstable in the presence of chloride or alkaline solutions. **Do NOT** mix or administer oxaliplatin with saline or other chloride-containing solutions. **Do NOT** administer other drugs or solutions in the same infusion line. Flush IV lines/catheters with Dextrose 5% in Water both before and after oxaliplatin administration.

#### 10.2.1.6 Toxicity

Please see package insert for detailed information. The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression. Three neurotoxicity syndromes have been seen: acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include paresthesias, dysesthesias, and hypoesthesia of the hands, feet, and perioral region. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain and a sensation of chest pressure have also been noted. Acute sensory neuropathy symptoms may be exacerbated by exposure to cold temperature or cold objects. Symptoms are reversible, usually resolving within 14 days and commonly recurring with further dosing. This syndrome has been observed in about 56% of subjects receiving oxaliplatin with 5-FU and leucovorin.

### 10.2.2 5-Fluorouracil (5-FU; fluorouracil)

Please refer to the package insert for complete product information.

#### 10.2.2.1 Availability

5-FU is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials.

#### 10.2.2.2 Preparation

Inspect for precipitate; if found, agitate or gently heat in water bath. These solutions may be prepared in D5W or 0.9% NaCl. 5-FU should not be mixed in the same solution with most parenteral antiemetics.

#### 10.2.2.3 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Slight yellow discolor does not usually indicate decomposition. Stability in ambulatory pumps varies according to the pump, manufacturer of drug, concentration and diluent. Please refer to appropriate reference sources for additional information.

#### 10.2.2.4 Administration

In this study, 5-FU is administered as a IV infusion over 46 hours (or per institutional standards).

#### 10.2.2.5 Toxicity

Nausea, diarrhea, vomiting (mild); stomatitis: 5-8 days after treatment initiation; myelosuppression: granulocytopenia (9-14 days); thrombocytopenia (7-14 days); Alopecia; loss of nails; hyperpigmentation; photosensitivity; maculopapular rash; urticaria; anaphylactoid reaction/anaphylaxis (hypotension, wheezing/stridor); palmar–plantar erythrodysesthesias: (42-82% receiving continuous infusion); CNS effects: cerebral ataxia (rare); cardiotoxicity: Myocardial infarction, angina; asymptomatic S–T changes 68%; ocular effects: excessive lacrimation and less commonly, tear duct stenosis.

#### 10.2.2.6 Drug Interactions

Leucovorin enhances the cytotoxicity of 5-FU by forming a more stable tertiary complex with thymidylate synthase. Concomitant administration of 5-FU with warfarin has been reported to result in increased INR/prolonged prothrombin time. Subjects receiving both drugs should be followed with weekly INRs.

### 10.2.3 Leucovorin Calcium (Folinic Acid)

Please refer to the package insert for complete product information.

In the case of a leucovorin shortage, levo-leucovorin may be administered (dose to be at site investigator's discretion). Other dosing alternatives may also be used during leucovorin shortage such as leucovorin 200 mg/$m^2$.

#### 10.2.3.1 Availability

Leucovorin calcium is commercially available in: 50 mg, 100 mg, 200 mg, 350 mg and 500 mg vials for reconstitution, and as a solution for injection in 50 mL vials at a concentration of 10 mg/mL.

#### 10.2.3.2 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Solutions reconstituted with BWI are stable for at least 7 days at room temperature. Solutions diluted for infusion are stable for 24 hours at room temperature and 4 days under refrigeration.

#### 10.2.3.3 Preparation

Leucovorin may be reconstituted with Bacteriostatic Water for Injection (BWI), Sterile Water For Injection, or bacteriostatic NaCl or NaCl. Solutions should be further diluted in D5W, 0.9% NaCl or Ringers solution for infusion over two hours.

#### 10.2.3.4 Administration

Leucovorin will be administered as an IV infusion over 30 minutes (or per institutional standards).

#### 10.2.3.5 Toxicity

The only adverse reactions associated with leucovorin are allergic reactions. These are extremely uncommon.

# 11. ADVERSE EVENTS

## 11.1 Definitions

### 11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

### 11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. **NOTE**: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject 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 inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Pregnancy
- Overdose

### 11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

### 11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

| | |
|---|---|
| **Unrelated** | The Adverse Event is ***not related*** to the drug(s) |
| **Unlikely** | The Adverse Event is ***doubtfully related*** to the drug(s) |
| **Possible** | The Adverse Event ***may be related*** to the drug(s) |
| **Probable** | The Adverse Event is ***likely related*** to the drug(s) |
| **Definite** | The Adverse Event is ***clearly related*** to the drug(s) |

## 11.2 Reporting

### 11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) and/or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

### 11.2.2 Serious Adverse Events (SAEs)

#### 11.2.2.1 Site Requirements for Reporting SAEs to Big Ten CRC Administrative Headquarters

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.

- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form (see Documents/Info tab in the EDC) to Big Ten CRC AHQ within **1 business day** of discovery of the event. The form will be sent electronically to Big Ten CRC AHQ at safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies of the SAE as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved, sites must electronically submit a follow up SAE Submission Form within a reasonable timeframe to Big Ten CRC AHQ at safety@hoosiercancer.org.

#### 11.2.2.2 Big Ten CRC AHQ Requirements for Reporting SAEs to Ipsen Biopharmaceuticals

Big Ten CRC AHQ will report SAEs to Ipsen Biopharmaceuticals within **1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Ipsen Biopharmaceuticals within one business day of receipt from a site. The information will be reported through one of the following communication methods:

Ipsen Pharmacovigilance contact: Ipsen Call Center
Telephone (24 Hours/7 Days): 855-463-5127
Fax: 855-631-0644
Emergency: drugsafety.USA@ipsen.com
Affiliate general PV mailbox: pharmacovigilance.USA@ipsen.com

#### 11.2.2.3 Sponsor-Investigator Responsibilities

Big Ten CRC AHQ will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

#### 11.2.2.4 Big Ten CRC AHQ Responsibilities for Reporting SAEs to FDA

The FDA has concluded this protocol is exempt from the requirements of an IND. Big Ten CRC AHQ will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

#### 11.2.2.5 IND Safety Reports Unrelated to this Trial

Ipsen Biopharmaceuticals will provide Big Ten CRC AHQ with IND safety reports from external studies that involve the study drug(s) per their guidelines. Big Ten CRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. Big Ten CRC AHQ will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from Big Ten CRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

## 12. STATISTICAL METHODS

### 12.1 Study Design

This is a phase II, single-arm, open-label, clinical study to investigate the efficacy and tolerability of a combination of liposomal irinotecan (nal-IRI) with oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX-nal-IRI) for treatment of patients with locally advanced pancreatic carcinoma (LAPC).

### 12.2 Endpoints

#### 12.2.1 Definition of Primary Endpoint

Disease control rate (DCR) as determined by the proportion of subjects with complete response, partial response, or stable disease, at 24 weeks following initiation of FOLFOX-nal-IRI.

#### 12.2.2 Definition of Secondary Endpoints

- Objective response rate (ORR) as determined by the proportion of subjects with either complete response or partial response as defined by RECIST 1.1 at 8 weeks, 16 weeks, and 24 weeks following initiation of FOLFOX-nal-IRI.
- Stable disease rate (SDR) as determined by the proportion of subjects with no progression of disease as defined by RECIST 1.1, at 8 weeks, 16 weeks, and 24 weeks following initiation of FOLFOX-nal-IRI.
- Rate of resectability as determined by the proportion of subjects who undergo surgical resection of tumors.
- The serum levels of CA 19-9 prior to initiation of chemotherapy and after every 2 cycles (every 4 weeks) following initiation of FOLFOX-nal-IRI.
- Progression-free survival (PFS) as determined by the time interval from the date of first dose of study drug to first documented disease progression or death from any cause, whichever occurs first, if evaluable.
- Overall survival (OS) as defined as the time interval from the date of the first dose of study drug to date of death from any cause.
- Safety and tolerability of FOLFOX-nal-IRI; Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.

- Quality of life as measured at baseline and after every 4 cycles (every 8 weeks) using the European Organization for Research and Treatment of Cancer Quality-of-Life Core Questionnaire (EORTC-QLQ-C30).

### 12.2.3 Definition of Exploratory Endpoints

- Effect of FOLFOX-nal-IRI DNA damage and apoptosis, in biopsied and surgically resected tumor tissue specimens (for subjects who undergo surgical resection of tumors), as determined by immunohistochemistry (or ELISA) for DNA damage/repair (phosphorylated histone H2AX, ɣH2AX), DNA double strand damage response (p53 binding protein, 53BP1), apoptosis (activated caspase 8 and caspase 3).
- Effect of treatment-induced DNA damage and apoptosis in peripheral blood lymphocytes (PBLs) before treatment and following every 4 cycles (8 weeks) of treatment, as determined by ɣH2AX and 53BP1, and serum biomarkers for apoptosis.
- Molecular profiling as determined by immunohistochemistry of biochemical markers (including expression level of topoisomerase 1, thymidine synthetase, ERCC1) and next-generation sequencing of genomic (exon) DNA (*BRCA1*, *BRCA2*, *TP53*, *CDKN2A*, *KRAS*), and correlation with treatment response based on CT scans and serum CA 19-9.
- Metabolic profiles of plasma before treatment and following every 4 cycles (8 weeks) of treatment, as determined by liquid chromatography/tandem mass spectrometry (by metabolomics core facility).
- The inter-institutional variability of the overall resectability rate as determined by central imaging analysis of tumor involvement of regional vasculature.

## 12.3 Sample Size and Accrual

It is assumed that LAPC patients have a DCR of 45% with standard of care, whereas LAPC patients will have DCR rate of 75% under the protocol in this study. A minimax Simon's two-stage design will be implemented with 12 patients evaluated in the first stage. If 5 or fewer responses are observed from these 12 patients, then the study will be stopped for futility. Otherwise, an additional 13 patients will be added yielding a total sample size of 25 patients. The study will be considered successful if 16 or more responses are observed in the 25 patients. This design comprises a type 1 error rate of 5% and a power of 80% when the true DCR is 75%.

Therefore, this study seeks to recruit 12 to 25 patients depending on results of the first stage evaluation. Assuming approximately 10% of the patients would not be evaluable, the target sample size is 28 patients.

## 12.4 Assessment of Safety

Any subject who receives at least one dose of treatment on this protocol will be evaluable for toxicity. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be used to assess safety.

## 12.5 Assessment of Efficacy

This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.

## 12.6 Data Analysis Plans

### 12.6.1 Analysis Plans for Primary Objective

The primary endpoint for this study is disease control rate (DCR).

In the study by Loehrer *et al*., 37 patients with LAPC treated with gemcitabine alone reported an objective response rate (ORR) of 5% and stable disease rate (SDR) of 35%, hence a DCR of 40%. As reported by Lakatos *et al*., 32 patients with LAPC were treated with a modified FOLFIRNOX protocol reported an ORR (partial regression only) of 18.8% and SDR of 56.2%, hence a DCR of 75%. For determining the sample size for this one-arm clinical trial, we will consider the study successful if the DCR is statistically significant from 45%.

### 12.6.2 Analysis Plans for Secondary Objectives

The Secondary Objectives will be analyzed as described in the section 12.2.2, Definition of Secondary Endpoints.

## 12.7 Interim Analysis/Criteria for Stopping Study

A single interim analysis for futility will take place when the 12$^{th}$ subject has completed 6 months of follow-up. The proportion of subjects that is tumor progression-free at 6 months will be assessed along with other efficacy and safety data in making the determination if the study should continue. If 5 or fewer responses are observed from these 12 patients, then the study will be stopped for futility. Otherwise, an additional 13 patients will be added yielding a total sample size of 25 patients. Accrual will continue during the interim analysis. Recruitment will be halted if futility is determined.

# 13. TRIAL MANAGEMENT

## 13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance with the Penn State Cancer Institute's (PSCI) DSMP.

Big Ten CRC AHQ oversight activities include:

- Review and process all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Submit data summary reports to the PSCI Internal Data Safety Monitoring Board for review as per their DSMP
- Submit data summary reports to the DSMB for review according to the site DSMP

## 13.2 Penn State Cancer Institute Internal Data Safety Monitoring Board

The PSCI DSMB will review the following on a semi-annual basis:

- Adverse event summary report
- Audit results, if applicable
- Data related to stopping/decision rules described in study design

- Study accrual patterns
- Protocol deviations

Documentation of these reviews will be provided to sponsor-investigator and Big Ten CRC AHQ. Issues of immediate concern by the PSCI Internal DSMB will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with Big Ten CRC AHQ to address the concerns.

### 13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Ipsen Biopharmaceuticals or its designee as well as inspection by appropriate regulatory agencies.

### 13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

## 14. DATA HANDLING AND RECORD KEEPING

### 14.1 Data Management

Big Ten CRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through a web-based clinical research platform compliant with Good Clinical Practices and Federal Rules and Regulations. Big Ten CRC AHQ personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

### 14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

### 14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/Big Ten CRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with local and federal regulations. No records will be destroyed until Big Ten CRC AHQ confirms destruction is permitted.

### 14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, Ipsen Biopharmaceuticals, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects's identity will remain confidential.

## 15. ETHICS

### 15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to Big Ten CRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

## 15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

## 15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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# 17. APPENDIX I

## Table 1 Prohibited Concomitant Medications

| Strong CYP3A4 inducers | Strong CYP3A4 inhibitors | UGT1A1 inhibitors |
|---|---|---|
| phenytoin | ketoconazole | ketoconazole |
| phenobarbital | grapefruit juice | atazanavir |
| carbamazepine | clarithromycin | gemfibrozil |
| St John's wort | indinavir | indinavir |
| | itraconazole | |
| | lopinavir | |
| | nefazodone | |
| | nelfinavir | |
| | ritonavir | |
| | saquinavir | |
| | telaprevir | |
| | voriconazole | |