RESILIENT: A **R**andomize**d**, Open Label Phase 3 **S**tudy of **I**rinotecan **L**iposome **I**nje**c**tio**n** (ONIVYDE®) versus **T**opotecan in Patients with Small Cell Lung Cancer Who Have Progressed on or after Platinum-based First-Line Therapy

IPSEN Bioscience, Inc

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SUMMARY OF CHANGES

The current version of the protocol (Version 8.0) was released on 07 October 2021. This protocol Version 8.0 includes all amendments, with summaries of changes from the protocol Version 2.0 included in the following appendices:

- Appendix V: Summary of Changes 03 April 2017 (Version 2.0) to 14 November 2017 (Version 3.0)
  - To streamline the phase II/III study design and allow sufficient statistical power for interim analysis
  - Appendix Va: Summary of Changes 14 November 2017 (Version 3.0) to 25 April 2018 (Version 3.1 France)
    - To incorporate country-specific request from French regulatory authority received during the clinical trial submission process
  - Appendix Vb: Summary of Changes 14 November 2017 (Version 3.0) to 10 May 2018 (Version 3.1 Germany)
    - To incorporate country-specific requests from German regulatory authority received during the clinical trial submission process
- Appendix VI: Summary of Changes: 14 November 2017 (Version 3.0) to 14 September 2018 (Version 4.0)
  - To incorporate country-specific requests from regulatory authorities received during the clinical trial submission process
  - To clarify eligibility criteria and protocol procedures
- Appendix VII: Summary of Changes 14 September 2018 (Version 4.0) to 04 December 2019 (Version 5.0).
  - To provide justification for dose level chosen for Part 2
  - To clarify protocol procedures
  - To update recommendations for management of chemotherapy-induced diarrhea
  - To clarify pregnancy follow-up period
  - To revise adverse event management guidelines
  - To update disease specific inclusion criteria.
- Appendix VIII: Summary of Changes 04 December 2019 (Version 5.0) to 15 April 2020 (Version 6.0).
  - To remove the futility interim PFS analysis as not required for decision on continuity of the study.
  - To clarify definition of length of SAE reporting (expressed differently in two different sections)
  - To clarify the sourcing of topotecan
  - Administration change to front cover fax number
- Appendix IX: Summary of Changes 15 April 2020 (Version 6.0) to 24 November 2020 (Version 7.0).
  - To update the statistical analysis to allow an assessment of the interim efficacy signal, confirming the promising results observed during the Part 1 by adding a descriptive analysis of ORR for efficacy at the time of the interim analysis of OS futility

- To amend the secondary and exploratory objectives for patient reported outcomes (PRO).
- To include reporting requirements and detail specifics to conduct of the study during the COVID-19 pandemic.
- To clarify eligibility criterion and protocol procedures.

• Appendix X: Summary of Changes 24 November 2020 (Version 7.0) to 07 October 2021 (Version 8.0).

- To include supplemental interim analysis of the efficacy and safety based on intent-to treat (ITT) population to fulfill FDA recommendation.

LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	5-fluoruracil
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BLQ	Below the limit of quantification
BOR	Best overall response
BSA	Body surface area
BUN	Blood urea nitrogen
CAV	Cyclophosphamide, doxorubicin, and vincristine
CBC	Complete blood count
CDX	Cell line derived xenograft
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum concentration
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
C#D#	Cycle #, Day #
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
D5W	Dextrose 5% in water
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EORTC-QLQ-C30	EORTC quality-of-life core 30 questionnaire
EORTC-QLQ-LC13	EORTC quality-of-life questionnaire; lung cancer supplement
ESMO	European Society of Medical Oncology
EQ-5D-5L	EuroQol 5 dimension health status questionnaire (5 level)
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
HR	Hazard ratio
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure

Abbreviation	Definition
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology System
ITT	Intent to treat
IV	Intravenous
LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
Nal-IRI	Irinotecan liposome injection; Liposomal irinotecan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease or disease progression
PFS	Progression free survival
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
QoL	Quality of life
QTcF	QT interval, Fridericia correction
RANO-BM	Response assessment in neuro-oncology brain metastases
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCLC	Small cell lung cancer
SmPC	Summary of medical product characteristics
SRC	Safety Review Committee
TEAE	Treatment emergent adverse event
TOP1	Topoisomerase-1
TTF	Time to treatment failure
ULN	Upper limit of normal
UGT	Uridine diphosphate glucuronosyl transferase
UGT1A1	Uridine diphosphate glucuronosyl transferase 1A1
UGT1A1*28	UGT1A1 pharmacogenetic variant *28
US	United States
USP	United States Pharmacopeia
USPI	United States package insert
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
WBC	White blood cell

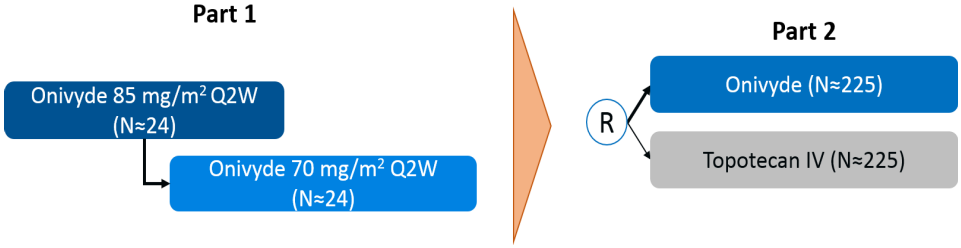
SYNOPSIS

Sponsor:	IPSEN Bioscience, Inc 650 East Kendall Street, Cambridge MA 02142- USA
Protocol Title:	RESILIENT: A Randomized, Open Label Phase 3 Study of Irinotecan Liposome Injection (ONIVYDE®) versus Topotecan in Patients with Small Cell Lung Cancer Who Have Progressed on or after Platinum-based First-Line Therapy
Protocol Number:	MM-398-01-03-04
Phase of Development:	3
Trial Locations:	Worldwide
Number of sites:	Approximately 137 sites will participate in the study.
Patient Population:	Patients with small cell lung cancer who have progressed on or after platinum-based first line therapy.
Estimated Number of Patients:	In Part 1 of the study, approximately 24 to 36 patients will be enrolled and in Part 2 of the study approximately 450 patients will be enrolled.
Objectives Part 1	**<u>Part 1 (single-arm; dose-ranging) Objectives:</u>** **Primary Objectives:** • Describe the safety and tolerability of irinotecan liposome injection monotherapy administered every 2 weeks • To determine the irinotecan liposome injection monotherapy dose (85 mg/m^2 or 70 mg/m^2 administered every 2 weeks) for Part 2 of this study. **(Note: all doses of irinotecan liposome injection refer to free base unless otherwise stated)** **Secondary Objectives:** To assess the preliminary efficacy of irinotecan liposome injection (at **either** the 85 mg/m^2 dose level **or** the 70 mg/m^2 dose level) as determined by: • Objective response rate (ORR) • Progression free survival (PFS) • Overall survival (OS). **Exploratory Objectives:** • To describe QTcF following treatment with irinotecan liposome injection. • To explore the biomarkers associated with toxicity and efficacy following treatment with irinotecan liposome injection in this patient population. • To describe the association between UGT1A1*28 and other UGT1A1 genotypes, SN-38 concentration and safety.

	• To evaluate the pharmacokinetics (PK) and the relationship between PK exposure and efficacy and safety following irinotecan liposome injection in this patient population. • To explore patient-reported outcomes (PROs) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC-QLQ-LC13), Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C), and EuroQol 5- dimension health status questionnaire (5 level) (EQ-5D-5L).
Objectives Part 2	**<u>Part 2 (two-arm randomized) Objectives:</u>** **Primary Objective:** To compare overall survival (OS) following treatment with irinotecan liposome injection with OS following treatment with IV topotecan. **Secondary Objectives:** To compare the following between the treatment arms: • Progression free survival (PFS) • Objective response rate (ORR) • Patient Reported Outcomes (PRO) • Safety profile. **Exploratory Objectives:** • To explore the biomarkers associated with toxicity and efficacy following treatment with irinotecan liposome injection in this patient population. • To describe the association between UGT1A1*28 and other UGT1A1 genotypes, SN-38 concentration (irinotecan liposome injection treated patients only) and safety. • To evaluate the pharmacokinetics and the relationship between pharmacokinetic exposure and efficacy and safety following irinotecan liposome injection in this patient population. • To compare the rate of development/time to development of central nervous system (CNS) progression and development of new CNS metastases between treatment arms. • To compare time to treatment failure between treatment arms. • To assess the proportion of patients with improvement in symptoms as measured by EORTC QLQ-C30/LC13 dyspnea scale. • To assess the proportion of patients with improvement in symptoms as measured by the EORTC QLQ-LC13. • To compare the effect of irinotecan liposome injection versus. topotecan on symptoms (other than dyspnea and cough), functioning and global health status as measured by EORTC-QLQ-C30, EORTC-QLQ-LC13 and EQ-5D-5L.
Study Design:	This study will be conducted in two parts: an open-label, single-arm, safety run-in period (Part 1) followed by a randomized period (Part 2) assessing irinotecan

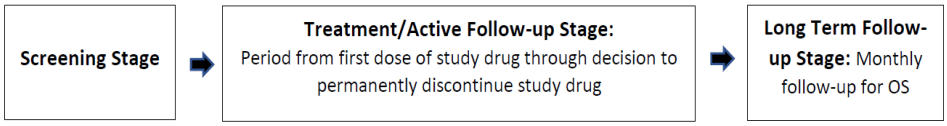
liposome injection versus IV topotecan in patients with small cell lung cancer (SCLC) who have progressed on or after platinum-based first line therapy.

Details of the study design for each part are as follows:



Note: Onivyde is also known as irinotecan liposome injection, liposomal injection or nal-IRI.

Each part will consist of three stages: screening stage, treatment/active follow-up stage and long-term follow-up stage. Once consented, patients will enter a screening stage. Upon first dose of study treatment in Part 1 or randomization (Part 2), patients will enter the treatment/active follow-up stage. Once a decision is made to permanently discontinue the patient from study treatment, a 30-day follow-up visit will occur and the patient will enter the long-term follow-up stage. The stages for this trial are outlined in the schematic below.

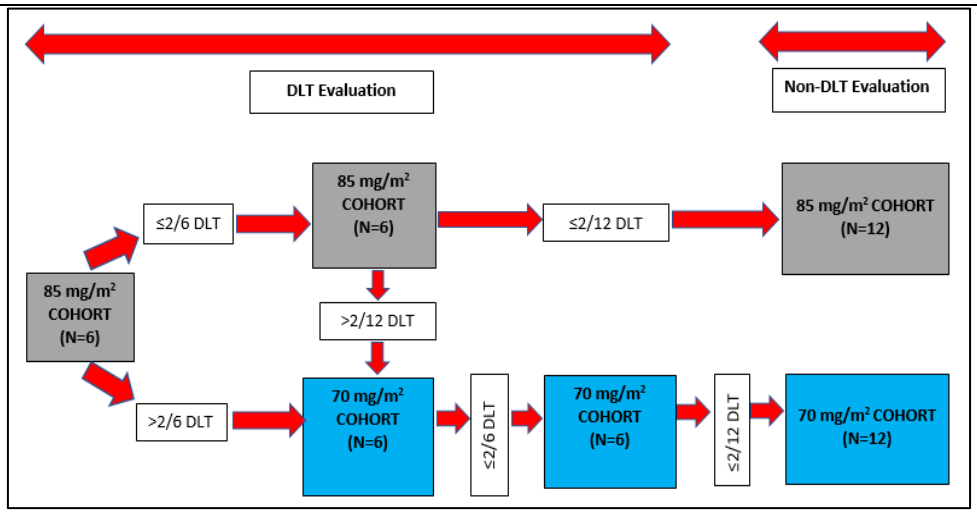


Part 1:

Part 1 is an open-label, single-arm, safety run-in evaluation of irinotecan liposome injection administered every 2 weeks intended to confirm the anticipated Part 2 regimen (85 mg/m^2), based on safety and preliminary efficacy. A contingency has been included for evaluation of irinotecan liposome injection at a dose level of 70 mg/m^2, should the higher dose level of 85 mg/m^2 result in unacceptable toxicity. At either dose level of irinotecan liposome injection up to 24 patients will be enrolled.

The safety assessment and the corresponding expansion will be conducted according to a "6+6" design followed by enrollment of an additional 12 patients (as described below). Patients will initially be treated with irinotecan liposome injection 85 mg/m^2 every 2 weeks. Dose limiting toxicities (DLTs) will be evaluated for the first 12 patients treated during the first 28 days of treatment (or up to 14 days after the second dose of study treatment if there is a treatment delay due to non-DLT related reasons).

- Among the first 6 patients receiving irinotecan liposome injection 85 mg/m^2 (i.e 85 mg/m^2 cohort), if ≤ 2 patients experience a DLT, another 6 patients will be enrolled into this cohort. Otherwise, enrollment into the 70 mg/m^2 cohort will be initiated.
- Among the first 12 patients receiving irinotecan liposome injection 85 mg/m^2, if ≤ 2 patients experience a DLT, this cohort will be expanded by 12 additional patients. Otherwise, the enrollment of the 85 mg/m^2 cohort will be stopped and the enrollment of the 70 mg/m^2 cohort will be initiated.



Note: all doses described are irinotecan liposome injection free base.

If the 70 mg/m^2 cohort is enrolled, the same "6+6" design followed by enrollment of an additional 12 patients, and the same DLT guidelines will be used as that for the 85 mg/m^2 cohort. If ≤ 2 patients among the first 12 patient receiving irinotecan liposome injection 70 mg/m^2 experience a DLT, then that dose level will be declared tolerable and this cohort will be expanded by 12 additional patients. Otherwise, additional dose reduction(s) may be considered.

Note that in either the 85 mg/m^2 cohort or the 70 mg/m^2 cohort, there will be no stopping rules based on DLT assessment; however, DLTs will continue to be assessed among the additional 12 patients recruited after the first 12 patients have completed DLT evaluation.

The decision of which dose to use for Part 2 will be made based on the totality of data from all patients treated in Part 1.

If a decision is made to terminate the irinotecan liposome injection 85 mg/m^2 dose level cohort (and instead initiate enrollment into the 70 mg/m^2 cohort) patients who are tolerating the 85 mg/m^2 dose level will remain at that dose level (unless subsequent toxicity requires a dose modification).

During the DLT evaluation period in either 85 mg/m^2 and 70 mg/m^2 cohort, the following adverse events (AEs) should be considered as DLTs if they occur during the first 28 days of treatment (or 14 days after the second dose of study treatment if there is a treatment delay and are deemed related to the study treatment by the investigator:

- Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal supportive therapy,
- Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity,
- Grade 3-4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or by infection,
- Any Grade 4 non-hematologic toxicity with the exception of the following:
  - Fatigue/asthenia lasting < 14 days,
  - Nausea and vomiting lasting ≤ 72 hours duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic treatment),

- Diarrhea ≤ 72 hours duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen),

- Grade 3 non-hematologic toxicity with the exception of the following:
  - Any gastrointestinal disorder and dehydration (with associated signs and symptoms) unless Grade 3 toxicity persists despite optimal medical management for > 72 hours,
  - Pain unless Grade 3 toxicity persists despite optimal medical management,
  - Fatigue, fever, flu like symptoms, infections and infestations,
  - Infusion reaction (and associated symptoms) unless it occurs following steroid premedication,
  - Hepatic and kidney function abnormalities, and electrolyte abnormalities unless they persist, despite optimal medical management.

The determination of whether an AE is considered a DLT will be made by the Safety Review Committee (SRC) comprising the Part 1 Investigators and the Medical Monitor(s) of the Sponsor. Other AEs, not meeting the DLT criteria above, that are deemed related to study treatment can also be considered a DLT event at the discretion of the SRC. Safety review meetings between investigators and sponsor will occur regularly during Part 1 of the study with at least monthly meetings, or more frequently, if required.

Safety and efficacy results from Part 1 will determine if the study proceeds to Part 2. The final decision to proceed to Part 2 will be made by the Sponsor in consultation with the study steering committee of the study, after consideration of all available efficacy and safety data from Part 1 of the study.

All patients in Part 1 will follow the same schedule of assessments as required for Part 2 detailed below.

Part 2:

Part 2 will be randomized, and assess the efficacy of irinotecan liposome injection versus IV topotecan. Approximately 450 eligible patients will be randomized in a 1:1 ratio between the experimental arm (Arm A: based on the findings of Part 1 [i.e. likely to be either 85 mg/m^2 or 70 mg/m^2 of irinotecan liposome injection]) and the control arm (Arm B: topotecan). Note that following assessment of the available safety and efficacy data from Part 1 the 70 mg/m^2 dose was chosen for Arm A. Patients will be randomized to the treatment arms using an Interactive Response Technology System (IRT) at a central location. Randomization will be stratified, based on the following factors:

- Region (North America vs. Asia vs. Other)
- Platinum sensitivity (sensitive vs. resistant)
- Performance status (ECOG 0 vs. 1)
- Prior immunotherapy (yes vs. no)

(Note: for platinum sensitivity, progression within 90 days from the completion of first-line platinum therapy is considered “platinum resistant” and the others “platinum sensitive”. Prior immunotherapy sensitivity should not be confused with platinum sensitivity).

Only region (North America vs. Asia vs. Other) and platinum sensitivity (sensitive vs. resistant) will be used for the stratified efficacy analysis.

	It is intended that all patients in Parts 1 and 2 will be treated until progressive disease or unacceptable toxicity (see Section 4.3.1). Patients may take a treatment holiday and resume study treatment under certain instances. Detailed rule for pausing and resuming study treatment can be found in Section 6.2.1. A modified visit schedule will operate during this treatment pause, however, tumor and quality of life assessments must be evaluated at the same frequency as during active treatment. Cross-over between treatment arms is not permitted. Upon permanent discontinuation of study treatment (defined as patients with progressive disease whilst receiving study treatment and/or those assessed by the Investigator as unable to continue or resume study treatment due to unacceptable toxicity), patients will return to the study site for a 30-day follow-up visit. After this visit, patients will continue to be followed for OS status by phone, email or a visit to the study site once every month until death or study closure, whichever occurs first. Tumor assessments will be performed every 6 weeks (± 1 week), using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1) (Parts 1 and 2) and Response Assessment in Neuro-oncology Brain Metastases (RANO-BM) criteria for CNS lesions (Part 2). Tumor assessment at screening and for all subsequent visits will be computed tomography (CT) with contrast (chest/abdomen required and pelvis [or other areas] if clinically indicated) and brain magnetic resonance imaging (MRI) with contrast. For patients who are allergic to IV contrast or cannot tolerate IV contrast due to impaired renal function or other issues, a non-enhanced CT or MRI is acceptable. Each follow-up tumor assessment should use the same assessment method as performed at screening, unless medically contraindicated. Patients who discontinue study treatment, for reasons other than disease progression, should continue to be followed-up until radiological documentation of progressive disease with the same schedule of tumor assessments (every 6 weeks ± 1 week) until radiological documentation of progressive disease or until the start of new anti-neoplastic therapy. The Sponsor will collect and store all tumor assessment images on all patients throughout the study. Progressive disease will be determined by local radiology review and/or investigator assessment. An independent central review of the scans will be performed at the discretion of the Sponsor to support potential early filing to regulatory authorities. All patients will be followed at least monthly for survival status until death, loss to follow-up or study closure, whichever comes first. A quality of life assessment will be performed using the EORTC-QLQ-C30, EORTC-QLQ-LC13, PGI-S, PGI-C and EQ-5D-5L questionnaires. Although the PGI-C and PGI-S are not specified as exploratory objectives in Part 2 they will serve as anchors deriving a within-patient meaningful change threshold in Part 2. All PRO instruments are required to be completed at screening, prior to dosing at 6-week intervals (and prior to any other assessment procedures) following start of treatment, at treatment discontinuation, at the 30-day follow-up visit. Patients who discontinue study treatment, for reasons other than disease progression, should continue to complete all QoL assessments every 6 weeks until radiological documentation of progressive disease or until the start of new anti-neoplastic therapy. The PGI-C is not included in the screening assessment. Adverse events will be evaluated according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For summary of AEs, events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 21.0 or later) at the start of the study. The primary analysis is planned when at least 350 OS events have occurred in Part 2. An interim analysis for OS futility is planned at approximately the 29%

	information time, after at least 100 OS events have occurred. A supplemental interim analysis is planned on data collected 24 weeks after the last patient has been randomized based on the ITT Population. At the timepoints of the interim analysis and supplemental interim analysis, ORR by blinded independent central review (BICR) tumor assessments will be analyzed descriptively: • by the independent DMC for the first 200 patients randomized in Part 2 of the study • for the full ITT population in the supplemental interim analysis. Details of BICR tumor assessment process and approach will be described in the imaging charter document. Details of the study-level type I error control are provided in the section on statistical methods and in the Statistical Analysis Plan (SAP). An independent DMC will be established to monitor data in Part 2 of the study, to evaluate the planned interim analysis for OS futility and to make recommendation to the Sponsor based on the results of this interim analysis over continuation or stoppage of the study. During the course of the study, regular review of safety data will be conducted in accordance with the DMC charter. The first safety review by the DMC will take place after the 30th patient is randomized and treated for at least one cycle or permanently discontinues study drug, whichever occurs first. The timing and details of subsequent data reviews will be detailed in the DMC charter. Items reviewed will include (but not limited to) safety events, results of interim analysis, any available results of PK testing and UGT1A1*28 genotype. Attention will be paid to determining whether any study procedure needs to be modified for patients who are homozygous for UGT1A1*28. **Pharmacokinetics** Sparse plasma samples for PK will be collected from all patients receiving irinotecan liposome injection (Part 1 and Part 2). **Biobanking** The exploratory endpoint comprises biobanking of samples for further analysis among patients who consent. Patient participation to consent to biobanking samples is optional. Analysis from the biobank samples will be performed outside the scope of the main study and reported separately.
Estimated Number of Patients	In Part 1 of the study, approximately 24 to 36 evaluable patients will be enrolled and in the Part 2 of the study approximately 450 patients will be enrolled.
Inclusion Criteria:	To participate in the study patients must meet the following inclusion criteria, and none of the exclusion criteria: **General Inclusion Criteria** 1. At least 18 years of age. 2. Able to understand and provide the study informed consent. 3. ECOG performance status of 0 or 1. 4. Life expectancy >12 weeks.

Disease Specific Inclusion Criteria

5. Histopathologically or cytologically confirmed small cell lung cancer according to the International Association for the Study of Lung Cancer (IASLC) histopathological classification. Mixed or combined subtypes according to the IASLC are not allowed.
6. Evaluable disease as defined by RECIST Version 1.1 guidelines (patients with non-measurable lesions are eligible).
7. Radiologically confirmed progression on or after first-line platinum based chemotherapy (carboplatin or cisplatin), or chemo-radiation including platinum-based chemotherapy for treatment of limited or extensive stage SCLC. In addition to platinum-based regimen, one line of immunotherapy as monotherapy or in combination in first or in second line setting is allowed.
8. Recovered from the effects of any prior chemotherapy, surgery, radiotherapy or other anti-neoplastic therapy (recovered to Grade 1 or better, with the exception of alopecia, peripheral neuropathy, or ototoxicity).

Hematologic, Biochemical and Organ Function Inclusion Criteria

9. During the Screening period, adequate bone marrow reserves as evidenced by:
    a. Absolute neutrophil count >1,500 cells/µL (1.5 x 10^9/L) without the use of hematopoietic growth factors within the immediately preceding 14 days;
    b. Platelet count >100,000 cells/µL (100 x 10^9/L);
    c. Hemoglobin >9 g/dL; transfusions are allowed.
10. Adequate hepatic function as evidenced by:
    a. Serum total bilirubin within normal range for the institution;
    b. Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x upper limit of normal (ULN) (≤ 5 x ULN is acceptable if liver metastases is present);
    c. Serum albumin ≥3.0 g/dL (≥ 30 g/L).
11. Adequate renal function as evidenced by a serum creatinine ≤1.5 x ULN and creatinine clearance ≥40 mL/min. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (except for patients with body mass index >30 kg/m^2 when lean body weight should be used instead):

$$\text{Serum Creatinine (mg/min)} = \frac{(140 - \text{Age (years)}) \times (\text{Weight (kg)})}{72 \times \text{Serum Creatinine (mg/dL)}} \times \text{Sex}$$

where Sex = 1 for male and 0.85 for females

12. Electrocardiogram without any clinically significant findings at screening, as per investigator's assessment.

	Additional Disease Specific Inclusion Criteria 13a Patients with certain types of asymptomatic CNS metastases that meet ALL the following criteria are eligible. a. Patients with asymptomatic CNS metastases prior to enrollment b. Prior radiation for CNS metastatic disease is completed ≥4 weeks prior to enrollment c. CNS metastases that are stable or have decreased according to the post radiation follow-up scan that is conducted at least 4 weeks after completion of radiation treatment for CNS lesion. d. Patients have discontinued corticosteroids or are on stable low-dose steroids (prednisone or equivalent 10 mg daily or less) for at least 1 week after completion of radiation for CNS lesion prior to enrollment.
Exclusion Criteria:	Patients must meet all the inclusion criteria listed above and none of the following exclusion criteria: **General Exclusion Criteria** 1. Any medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results. 2. Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a serum pregnancy test. Females of childbearing potential are defined as fertile, following menarche and until becoming postmenopausal unless permanently sterile. Postmenopausal women are defined as those that have an absence of menstruation for at least 2 years. If necessary, follicle stimulating hormone results >50 IU/L at screening are confirmatory in the absence of a clear postmenopausal history. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Male patients must agree to use condoms during the study and for 4 months following the last dose of study drug. Female patients of reproductive potential must agree to use a highly effective method of birth control, during the study and for 1 month following the last dose of study drug. **Disease Specific Exclusion Criteria** 3. Patients with large cell neuroendocrine lung carcinoma. 4. Patients who have received any of the following treatments: a. Prior treatment regimens with irinotecan, topotecan or any other topoisomerase I inhibitor including investigational topoisomerase I inhibitors; b. Retreatment with platinum-based regimen after relapse of first-line platinum-containing therapy; c. Any antibody-drug conjugates or molecular targeted agents (e.g. poly ADP-ribose polymerase inhibitors), either alone or in combination with other treatments;

	d. More than one line of prior immunotherapy; e. Any other additional regimen of prior cytotoxic chemotherapy, not described above. 5. Patients with a history (any grade) of immunotherapy induced colitis or pneumonitis, based on clinical assessment and/or confirmed by biopsy. 6. Patients with any of the following CNS metastases: a. Patients who have developed new or progressive brain metastasis within three months following prophylactic and/or therapeutic cranial radiation (whole brain or stereotactic radiation) as defined by imaging; b. Patients with symptomatic CNS metastases; c. Patients with carcinomatous meningitis. 7. Unable to discontinue the use of strong CYP3A4 or UGT1A1 inhibitors at least 1 week or strong CYP3A4 inducers at least 2 weeks prior to receiving the first dose of irinotecan liposome injection. 8. Have a previous or concurrent cancer that is distinct in primary (non-pulmonary) site or histology, except carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors (Ta and Tis [carcinoma in situ]) or any previous cancer curatively treated with last specific treatment >3 years ago without evidence of recurrence. 9. Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives (whichever is less) of the investigational agent prior to the first scheduled day of dosing in this study. **<u>Hematologic, Biochemical and Organ Function Exclusion Criteria</u>** 10. Severe cardiovascular and pulmonary disease (e.g. myocardial infarction, unstable angina pectoris, coronary angioplasty or stenting, deep vein thrombosis, stroke, pulmonary fibrosis, active uncontrolled bleeding, or a known bleeding diathesis) less than 6 months before inclusion. 11. New York Heart Association Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure. 12. Active infection (e.g. acute bacterial infection, tuberculosis, active hepatitis B/C or active human immunodeficiency virus) which in the Investigator's opinion might compromise the patient's participation in the trial or affect the study outcome. 13. Known hypersensitivity to any of the components of irinotecan liposome injection, other liposomal products, or topotecan. 14. Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > Grade 1. **<u>Additional Disease Specific Exclusion Criterion (only applicable in France, per request of French Regulatory Authorities)</u>** 15. Patients who, per investigator assessment, are suitable for a second line platinum-based regimen following relapse after first-line platinum-based therapy.
Length of Study:	The study will end when all patients are off study drug treatment and at least 350 OS events have occurred in Part 2

Study Assessments:	See Schedule of Assessments
Study Treatment	**Irinotecan liposome injection:** **Part 1: (single-arm, dose-ranging)** • Irinotecan liposome injection 85 mg/m^2 (strength expressed as irinotecan free base; approximately equivalent to 100 mg/m^2 of the hydrochloric trihydrate salt) IV over 90 minutes, every 2 weeks in a 6-week cycle **OR** • Irinotecan liposome injection 70 mg/m^2 (strength expressed as irinotecan free base; approximately equivalent to 80 mg/m^2 of the hydrochloric trihydrate salt) IV over 90 minutes, every 2 weeks in a 6-week cycle. **Part 2 (two-arm, randomized):** • Irinotecan liposome injection 85 mg/m^2 (strength expressed as irinotecan free base; approximately equivalent to 100 mg/m^2 of the hydrochloric trihydrate salt) IV over 90 minutes, every 2 weeks in a 6-week cycle (unless deemed unacceptable in Part 1, in which case the 70 mg/m^2 dose level [strength expressed based on irinotecan free base; approximately equivalent to 80 mg/m^2 of the hydrochloric trihydrate salt] will be utilized IV over 90 minutes, every 2 weeks in a 6-week cycle). Note that following assessment of the available safety and efficacy data from Part 1 the 70 mg/m^2 dose level will be utilized for Part 2. • Topotecan 1.5 mg/m^2: IV over 30 minutes daily for 5 consecutive days, every 3 weeks in a 6-week cycle. Up to three dose reductions of irinotecan liposome injection or up to two dose reductions of topotecan per patient are permitted due to toxicities. Dose delays are permitted to allow recovery from treatment-associated toxicities. Prophylactic antibiotics are recommended for patients at high risk of infectious complications. Prophylactic granulocyte colony stimulating factors should be considered. For further details on dose reductions and supportive care measures, please refer to Section 5.3.
Investigational Product:	Irinotecan liposome injection (also known as liposomal irinotecan, nal-IRI, MM-398, PEP02, BAX2398 and ONIVYDE®) is a sterile, white to slightly yellow opaque isotonic liposomal dispersion. Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrosofate salt. It will be supplied as sterile, single-use vials containing 43 mg irinotecan free base at a concentration of 4.3 mg/mL. Irinotecan liposome injection must be stored refrigerated (2 to 8°C, 36 to 46°F) with protection from light. Do not freeze.
Sample Size	**<u>Part 1:</u>** Up to 36 patients will be evaluated in Part 1. Up to 12 patients per dose level of irinotecan liposome injection may be treated at either 85 mg/m^2 or 70 mg/m^2 and one of these two dose levels will subsequently be expanded to a total of 24 patients. A dose level of irinotecan liposome injection will be determined to have an acceptable toxicity profile if there are ≤2 DLTs in the first 12 patients evaluated.

	A total of 24 patients (at the eventually selected dose level of irinotecan liposome injection) is considered sufficient to provide a preliminary assessment of efficacy endpoints, for the purposes of determining whether to proceed to Part 2. **<u>Part 2:</u>** The primary endpoint is OS. A total of 450 patients will be randomized in a 1:1 ratio to the two treatment arms. Follow-up until at least 350 OS events are observed across the two treatment arms provides at least 87% power to detect a true hazard ratio of HR $\leq$ 0.714 (median OS: 7.5 vs 10.5 months) using a stratified log-rank test (stratified by region (North America vs. Asia vs. Other) and platinum sensitivity (sensitive vs. resistant)) with overall 1-sided significance level of 0.025 (adjusted for the interim analysis). Assuming enrollment over 24 months with a ramp-up to a maximum of 21 patients per month and lost-to-follow-up rate of 5% across both treatment arms, the timing of the primary analysis is expected to be at 37 months. An interim OS analysis for futility will be conducted when approximately 29% of the planned final number of OS events (i.e., approximately 100 of 350 OS events) has been observed in the ITT population. At the timepoint of the interim analysis, ORR by BICR tumor assessments will be analyzed descriptively by the independent DMC for the first 200 patients randomized in Part 2 of the study. The independent DMC will notify the Sponsor if pre-specified criteria for ORR are met. A supplemental interim analysis is planned on data collected 24 weeks after the last patient has been randomized based on the ITT population to fulfill FDA recommendation. At this timepoint, OS and ORR (supported by DOR) will be summarized descriptively. Note: detailed methodology is further described in the SAP.
Statistical Considerations and Data Reporting:	**General:** Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum). **<u>Part 1</u>:** The efficacy and safety of irinotecan liposome injection in Part 1 will be reported descriptively. In addition, AEs occurring in Part 1 of the study will be described in detail. Patients enrolled and treated with at least one dose of irinotecan liposome injection will comprise the Part 1 safety and efficacy population. **<u>Part 2</u>:** Patients randomized in Part 2 will comprise the ITT population. This will be the population used to evaluate the efficacy (OS, PFS, ORR) of the experimental arm. In the ITT analyses of efficacy, each patient will be considered according to the randomized treatment assignment. Patients who received any part of any study drug will define the Part 2 safety population.

For stratified analyses, stratification factors will be the randomization stratification factors of region (North America, Asia, Other) and platinum sensitivity (sensitive, resistant).

Primary Efficacy Analysis (Part 2):

Overall Survival

Overall survival is defined as the number of months from randomization in Part 2 to the date of death. Patients without observed death at the time of the primary analysis will have OS censored according to the last recorded date alive.

The primary analysis will be performed using a stratified log-rank test (stratified by region and platinum sensitivity) comparing the OS difference between two treatment arms with level of significance controlled at the one-sided 0.025 level. Kaplan-Meier methods will be used to estimate median OS (with 95% confidence intervals (CI)) and to display OS time graphically. A stratified Cox proportional hazards model will be used to estimate hazard ratio and its corresponding 95% CI. Sensitivity analyses for OS will be described in the SAP.

An interim analysis of OS for futility (at approximately 29% of planned OS events) is planned. To control type I and type II errors, the planned interim analysis will utilize an alpha and (non-binding) beta spending function approach with Hwang-Shih-Decani spending and γ parameter equal to -4.5 for each type I error and $\gamma = -1$ for type II error (Hwang, 1990).

A supplemental interim analysis is planned on data collected 24 weeks after the last patient has been randomized based on the ITT population to fulfill FDA recommendation. At this timepoint, OS and ORR (supported by DOR) will be summarized descriptively.

Key Secondary Efficacy Analyses (Part 2):

Key secondary endpoints are PFS, ORR and change from baseline in patient reported symptoms (dyspnea and cough).

Key secondary endpoints will be tested no more than once. To control the overall Type I error rate for the comparison between irinotecan liposome injection and topotecan for the primary and secondary endpoints, a hierarchical approach will be applied to the statistical testing of the secondary endpoints. The statistical inference for the first secondary endpoint of PFS (by BICR) will only be performed if the primary endpoint (OS), is statistically significant. The second secondary endpoint of ORR (by BICR) will only be tested if PFS is statistically significant. Similarly, the PRO endpoints will only be tested if ORR is statistically significant. Any parameter which is not statistically significant will be regarded as descriptive and exploratory.

Progression-free survival:

Progression-free survival is the time from randomization in Part 2 to the first documented objective disease progression (PD) using RECIST Version 1.1 (or RANO-BM criteria for CNS lesions) or death due to any cause, whichever occurs first. Determination of PFS will be based on BICR tumor assessment, with PFS based on investigator tumor assessments as a sensitivity analysis. If neither death nor progression is observed, data will be censored on the date of the last observed tumor assessment date. Patients without a valid tumor response evaluation at enrollment/randomization will be censored on the date of

enrollment/randomization. Patients starting a new anti-cancer treatment prior to documented PD will be censored at the date of the last observed tumor assessment prior to start of the new treatment. Patients with documented PD or death after an unacceptable long interval (i.e. 2 or more missed or indeterminate scheduled assessments) will be censored at the time of the last observed non-PD tumor assessment date prior to progression or death. Details of data handling for censoring of PFS will be provided in the SAP.

The difference in PFS between treatments will be evaluated using a stratified log-rank test (stratified by region and platinum sensitivity). Kaplan-Meier methods will be used to estimate median PFS (with 95% CI) and to display PFS time graphically. A stratified Cox proportional hazards model will be used to estimate the PFS hazard ratio and its corresponding 95% CI. Sensitivity analyses for PFS will be described in the SAP.

Objective Response:

Objective response rate is the proportion of patients who achieve partial response (PR) or complete response (CR) according to RECIST Version 1.1 guidelines (or RANO-BM criteria for CNS lesions, Part 2). An estimate of the ORR and its 95% CI will be calculated. The difference in ORR between treatment groups will be compared using Cochran-Mantel-Haenszel method, stratified by region and platinum sensitivity.

In addition to investigator assessment, a BICR review of the tumor assessment images will be performed for all patients included in the study, and more specifically at the time of:

- the interim analysis, for the descriptive analysis of ORR based on the first 200 patients randomized in both arms (i.e. approximately 100 patients from each arm) as well as for the patients included in Part 1 and treated with the selected dose for Part 2.
- the supplemental analysis, for tumor images for all randomized patients collected 24 weeks after the last patient has been randomized.

A final formal test on secondary endpoint ORR will be based on BICR tumor assessment, with ORR based on investigator tumor assessments as a sensitivity analysis.

Patient Reported Outcomes:

The secondary endpoints below are included in the testing hierarchy:

- Change from baseline to Week 12 in EORTC QLQ-C30/LC13 dyspnea scale
- Change from baseline to Week 12 in EORTC QLQ-LC13 cough scale

Safety Analysis:

Safety analyses (AEs and laboratory analyses) will be performed using the safety population, defined as all patients receiving any study drug. Treatment assignment will be according to actual treatment received. Adverse events will be coded using MedDRA (Version 21.0 or later). Severity will be graded according to the NCI CTCAE Version 5.0.

Treatment-emergent adverse events (TEAEs) are defined as any AEs reported from the date of first study drug exposure to 30 days after the last date of study drug exposure. Frequency and percentages of patients will be summarized for: any grade TEAE, Grade 3 or higher TEAE, study-drug related TEAE, serious TEAE, TEAE

	leading to dose modification, TEAE leading to study drug discontinuation, death and TEAE leading to death. Adverse events will be summarized by system organ class and preferred term. All AE data will be listed by patient. Laboratory data will be summarized according to parameter type. Where applicable, toxicity grading for laboratory safety parameters will be assigned based on NCI CTCAE Version 5.0 criteria. **QTcF Analyses:** The potential of QTcF prolongation with irinotecan liposome injection treatment will be evaluated in patients receiving irinotecan liposome injection in Part 1 of this study. For the primary QTcF prolongation analysis, the predicted changes in QTcF will be obtained from the exposure-QTcF relationship using mixed-effect modeling. Sensitivity analyses will be conducted by evaluating by timepoint and categorical analyses. **Pharmacokinetics and Pharmacodynamics Analysis:** Pharmacokinetics of total irinotecan and SN-38 will be quantified from the concentrations from plasma samples using nonlinear mixed effect modeling. The initial PK analysis will use the empirical Bayesian estimation, however, additional covariate analyses will be performed to evaluate alternative baseline factors specific to SCLC. The resulting PK estimates will be used to evaluate the association between PK and pharmacodynamics (efficacy and safety endpoints).

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Small Cell Lung Cancer

Lung cancer is the leading cause of cancer deaths worldwide. Small cell lung cancer (SCLC) accounts for about 15% of lung cancers overall and is a particularly aggressive neoplasm with a 5-year survival of <10%. Little progress has been made in improving outcome for this malignancy over the last 30 years.

Small cell lung cancer is classified into limited and extensive stage disease based on the extent of the disease. Approximately 30% of patients with SCLC are diagnosed with limited stage disease, and are typically treated with a combination of radiation and chemotherapy (Morabito 2014). With current treatments only ~20% of patients with limited stage disease have potential to be cured (Dowell, 1999). Extensive stage disease remains incurable with an expected median survival of 7 to 9 months (Morabito, 2014). Extensive stage disease is typically first treated with a combination of a platinum (carboplatin or cisplatin) plus etoposide in the US and EU (NCCN guidelines; Früh et al, 2013) or irinotecan plus cisplatin in Japan (NCC Japan Annual Report, 2013). About 50-90% of patients with extensive stage disease respond to initial treatment (Morabito, 2014); however, patients rapidly relapse and develop resistance. Those that have progressed within 90 days from the completion of first-line platinum therapy are considered "platinum resistant" and the others "platinum sensitive" (prior immunotherapy sensitivity should not be confused with platinum sensitivity). Because most patients experience relapse or disease progression after initial response to chemotherapy, subsequent therapy is often required with the hope of symptom palliation or prolongation of survival. For patients who progress >6 months from the completion of first-line therapy, re-challenge with the same drugs used as the initial treatment has been reported to result in potential benefit. Although both the European Society for Medical Oncology (ESMO) guidelines (Früh et al, 2013) and the 2020 NCCN guidelines suggest the use of the original first line regimen when relapse occurs after 6 months, the level of evidence for this recommendation is based on studies conducted in the 1980s (Postmus, 1987; Giaccone, 1987) with small numbers of patients (level V evidence in the ESMO guideline, e.g. studies without control group, case reports, experts' opinion). Additionally, a recent study by Wakuda (2015) showed that relapsed patients re-challenged with the first line regimen had similar outcomes to those receiving single-agent chemotherapy. This platinum re-challenge approach is utilized mainly due to very limited treatment options for recurrent SCLC.

The topoisomerase I (TOP 1) inhibitor topotecan is the only agent approved for second-line therapy in the United States (US) and Europe. A study by von Pawel (1999) compared intravenous topotecan with a regimen of cyclophosphamide, doxorubicin, and vincristine (CAV) for patients with recurrent SCLC. Topotecan treatment reduced symptoms to a greater degree than CAV and was associated with less hematologic toxicity, although it failed to provide a survival benefit. The combination of oral topotecan plus best supportive care has shown both survival and quality-of-life benefits compared with best supportive care alone in patients with relapsed SCLC (O'Brien, 2006). In Japan, in addition to topotecan, amrubicin is also approved but it failed to gain approval elsewhere, following its failure to demonstrate superior efficacy in a large phase III study conducted in Western patients (von Pawel, 2014).

Irinotecan is also an active and useful agent in SCLC. Superior overall survival (OS) for irinotecan plus cisplatin over cisplatin plus etoposide was noted in a Phase 3 study conducted in first line extensive stage patients in Japanese patients (Noda, 2002). Irinotecan is not approved for SCLC outside of Japan because a study in Western patients failed to replicate the superior efficacy seen in Japanese patients (Hanna, 2006). However, three additional phase III studies of irinotecan plus a platinum versus etoposide plus a platinum in the first line setting

have shown a trend of increased OS for patients receiving irinotecan combinations including one study that met statistical significance (Zatloukal, 2010; Lara, 2009; Hermes, 2008). In the second line setting, single agent irinotecan has been evaluated in a few small studies with reported objective response rate (ORR), time to treatment progression, and OS in the range of 0-47%, 1.7-2.6 months and 4.6 months, respectively, (Pallis, 2009; Masuda, 1992; Sevinc, 2011) with similar outcomes to that of topotecan (von Pawel, 2014). Based on these and other studies, irinotecan is included in major treatment guidelines for the treatment of patients with SCLC. Irinotecan plus either cisplatin or carboplatin is listed as possible first line regimen as well as irinotecan monotherapy in second line in the National Comprehensive Cancer Network (NCCN) guidelines (2020 NCCN guidelines). ESMO guidelines list irinotecan plus cisplatin as an alternative first line regimen for those patients for whom etoposide is contraindicated (Früh, 2013).

1.2 Study Rationale

1.2.1 Rationale for Evaluating Irinotecan Liposome Injection in SCLC

The rationale for testing irinotecan liposome injection (also known as liposomal irinotecan, nal-IRI, MM-398, PEP02, BAX2398, and ONIVYDE®) in patients with SCLC is based on targeting a validated drug target (TOP1), supportive non-clinical data, the concordance between SCLC biology and the proposed irinotecan liposome injection mechanism of action and prior clinical data for non-liposomal irinotecan in other indications. Based on these factors it is hypothesized that irinotecan liposome injection has the potential to improve upon the clinical activity of both topotecan and non-liposomal irinotecan.

Topoisomerase I is a validated drug target in SCLC and is the target of topotecan, an approved agent in SCLC. SN-38, the active metabolite of irinotecan (and irinotecan liposome injection), is also known to target TOP1. Deoxyribonucleic acid (DNA) topoisomerases are a class of enzymes involved in the regulation of DNA supercoiling. Type I topoisomerases change the degree of supercoiling of DNA by causing single-strand breaks and re-ligation. Inhibition of TOP1 stabilizes the complex between TOP1 and DNA which collides with moving DNA replication forks, eventually leading to double stranded DNA damage and ultimately cell death. It is well established that increased cytotoxicity of TOP1 inhibitors is associated with sustained exposure. Liposomal delivery of irinotecan, a prodrug of SN-38, provide a mechanism for sustained inhibition of TOP1.

Nonclinical data support the use of irinotecan liposome injection in SCLC, as described in Section 1.2.4. The biology of SCLC is well-matched with the irinotecan liposome injection proposed mechanism of action, which involves liposomal deposition in tumor tissue through leaky vasculature, followed by drug release either interstitially or after cellular uptake by phagocytic cells and subsequent conversion of irinotecan to SN-38. Irinotecan liposome injection deposits in and delivers irinotecan to tumors in SCLC models to a similar or greater extent than other tumor types and results in therapeutically relevant levels of tumor SN-38. Irinotecan liposome injection demonstrated anti-tumor activity in multiple xenograft models of SCLC at clinically-relevant dose levels and, importantly, demonstrated greater anti-tumor activity than irinotecan and topotecan. Finally, irinotecan liposome injection demonstrated greater anti-tumor activity than irinotecan and topotecan in a model of second line SCLC in which tumor has previously progressed on prior carboplatin plus etoposide.

Irinotecan liposome injection has not yet been evaluated in clinical trials in patients with SCLC. However, the availability of clinical efficacy data for non-liposomal irinotecan monotherapy in this indication (described in Section 1.1), the overlapping mechanism of action of (non-liposomal) irinotecan and irinotecan liposome injection [mediated through the same active SN-38) metabolite] and the anticipated predictable safety profile of irinotecan liposome

injection collectively suggest that extrapolation from previous experience with non-liposomal irinotecan is an appropriate means of identifying a suitable starting dose level of irinotecan liposome injection in the context of SCLC. Based on these considerations, the current study comprises an initial non-randomized portion (safety run-in) where patients will be treated with irinotecan liposome injection at a dose level of 85mg/m^2 every 2 weeks in Part 1 in order to ensure that the safety of the proposed regimen (85 mg/m^2) is acceptable prior to proceeding to the randomized Part 2 of the study. Additional data (discussed in Section 1.2.2) derived from clinical experience of irinotecan liposome injection in malignant indications other than SCLC, at dose levels comparable to, or in excess of those included within the current study, further support the proposed dose level of 85mg/m^2.

However, a contingency has been included for subsequent safety evaluation of a lower dose level of irinotecan liposome injection (70 mg/m^2 every 2 weeks) should the 85 mg/m^2 level prove to have unacceptable toxicity. Additionally, preliminary efficacy will be defined in a total of 24 patients at the eventual Part 2 dose level of irinotecan liposome injection, in order to permit an overall assessment of safety and efficacy prior to commencement of Part 2. It is, therefore, considered that the initial safety and preliminary efficacy evaluation of irinotecan liposome injection, at one of two possible dose levels, provides a robust basis for progressing to Part 2 of the study. Additional risk control measures have been incorporated into Part 2 through a futility analysis for OS combined with a prospective program of safety review by an independent Data Monitoring Committee (DMC). Therefore, the study design facilitates rapid progression to a registration directed trial phase in this difficult to treat disease, whilst retaining sequential ongoing risk-benefit assessment during the conduct of the study, thus protecting patient safety and preserving the scientific integrity of the study.

1.2.2 Rationale for Evaluating 85 mg/m^2 Every 2 Weeks Monotherapy Dose of Irinotecan Liposome Injection

The rationale for evaluating 85 mg/m^2 free base dose every 2 weeks is supported by clinical studies for non-liposomal irinotecan HCl, the clinical pharmacology of irinotecan liposome injection and data from clinical studies of irinotecan liposome injection.

In early clinical studies of non-liposomal irinotecan HCl there is convincing evidence of a dose-response relationship (Van Cutsem, 2005). In phase I studies of non-liposomal irinotecan HCl, increased tumor responses were seen at higher doses (Merrouche, 1997; Abigerges, 1995) and the dose-efficacy relationship has been further supported by subsequent population pharmacokinetic (PK) analyses (Chabot, 1995).

The clinical pharmacology of irinotecan liposome injection indicates a dose-efficacy relationship supporting the evaluation of a higher than currently approved biweekly dose of 70 mg/m^2 (approved in combination with 5-fluorouracil (5-FU) and leucovorin (LV)). In metastatic pancreatic cancer, patients in the NAPOLI-1 study treated with irinotecan liposome injection 70 mg/m^2 + 5-FU/LV, a higher exposure of unencapsulated SN-38 (uSN38; in the form of time above effective concentration and average concentration) was found to have association with better efficacy in terms of OS, PFS, and ORR therefore, a higher dose of irinotecan liposome injection has the potential for further improved efficacy. In the irinotecan liposome injection arm of the randomized phase II PEP0206 study, 44 patients with metastatic gastric cancer were treated with irinotecan liposome injection monotherapy dosed at 100 mg/m^2 free base every 3 weeks. The ORR in the intent to treat (ITT) population in the irinotecan liposome injection arm was 13.6%. Intra-patient dose escalation was permitted for patients who tolerated 100 mg/m^2 irinotecan liposome injection (every 3 weeks) without Grade 2 or above toxicity. Five patients received 130 mg/m^2 free base dose after first receiving the 100 mg/m^2 dose. Three out of the five patients exhibited confirmed partial response and two had stable

disease. These results are suggestive of dose-efficacy relationship and provide further support for evaluation of an 85 mg/m^2 every 2 weeks regimen of irinotecan liposome injection in this trial in patients with SCLC.

Clinical studies of irinotecan liposome injection and clinical pharmacology support the potential safety of the 85 mg/m^2 dose of irinotecan liposome injection administered every two weeks. In a phase I study (PIST-CRC-01), in patients with advanced refractory colorectal carcinoma, a dose of irinotecan liposome injection monotherapy of 86 mg/m^2 every 2 weeks was well tolerated and active. In a cohort of 6 patients treated at this dose level, there was 1 dose limiting toxicity (DLT) (Grade 3 diarrhea) and 1 partial response noted (see Section 1.3.2).

1.2.3 Rationale for Intravenous Topotecan as Control

The choice of intravenous topotecan as the control arm for the randomized portion of this study was based on its inclusion in multiple clinical practice guidelines, its approval in both the US for use in platinum-sensitive patients who progressed after first-line chemotherapy and in the European Union (EU) for patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate, and its widespread clinical use in this disease setting. In patients with relapsed or refractory SCLC, the administration of second line single agent chemotherapy, including topotecan, is recommended by the NCCN (2020 NCCN guidelines) and by the American Society of Clinical Oncology guidelines (Rudin, 2016). The European Society of Medical Oncology guidelines (Früh, 2013) recommend oral or intravenous topotecan for patients who have platinum-resistant or sensitive relapsed SCLC. Intravenous topotecan is approved in the US for patients with SCLC that are platinum-sensitive and have progressed on first-line therapy (Topotecan USPI), and in the EU for patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate (Topotecan SmPC).

It is worth noting that the use of intravenous topotecan for platinum-sensitive patients is potentially controversial due to guidelines suggesting re-challenge with the first line regimen. Although both the ESMO guidelines (Fruh et al, 2013) and the 2020 NCCN guidelines suggest the use of the original first line regimen when relapse occurs after 6 months, the level of evidence for this recommendation is based on studies conducted in the 1980s (Postmus, 1987; Giaccone, 1987) with small numbers of patients (level V evidence in the ESMO guideline, e.g. studies without control group, case reports, experts' opinion). Additionally, a recent study by Wakuda, et al (2015) showed that relapsed patients re-challenged with the first line regimen had similar outcomes to those receiving monotherapy chemotherapy. Finally, intravenous topotecan has been used as a control arm in recently completed phase II and phase III studies in second-line SCLC (cabazitaxel vs. intravenous topotecan (Evans, 2015) and amrubicin vs. intravenous topotecan (von Pawel, 2014)) indicating both its acceptability to the clinical community and the feasibility of enrolling a study with this control arm.

Oral topotecan will not be allowed in the control arm, as intravenous topotecan is the predominantly prescribed topotecan formulation (>90%) in US clinical practice (Intercontinental Marketing Services claims data) and appears to be the preferred topotecan formulation in clinical practice outside of the US as well, as indicated to the Sponsor by lung cancer clinical experts. Finally, intravenous topotecan will result in greater control over compliance than oral administration and will further minimize heterogeneity in the control arm.

1.2.4 Nonclinical Data Supporting Evaluation of Irinotecan Liposome Injection in Small Cell Lung Cancer

The mechanism of action of irinotecan liposome injection comprises extended plasma circulation (as compared to non-liposomal irinotecan HCl), deposition into tumor tissue via the vasculature, uptake by phagocytic cells, release of drug and conversion of irinotecan to its active

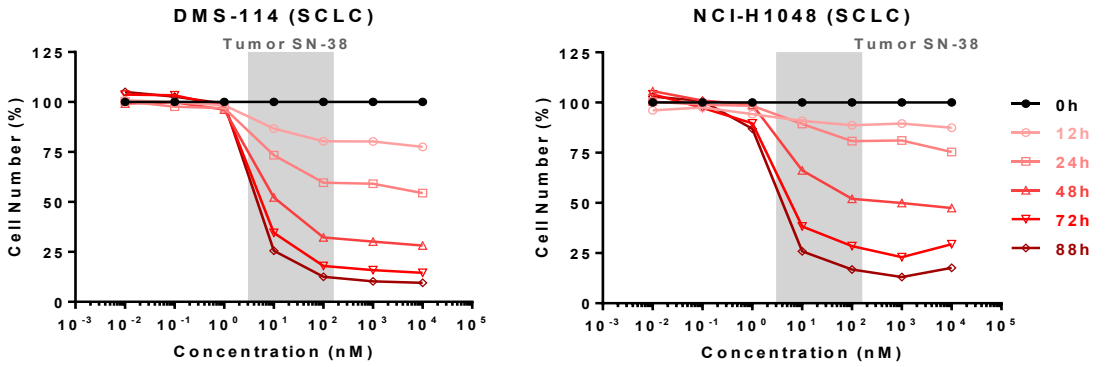
metabolite SN-38. Sustained tumor-derived SN-38 delivery by irinotecan liposome injection leads to sustained TOP1 inhibition, resulting in subsequent DNA damage and tumor cell death (Kalra, 2014).

The following *in vitro* and *in vivo* data highlight aspects of the proposed mechanism of action of irinotecan liposome injection and illustrate the potential activity of irinotecan liposome injection in comparison to non-liposomal irinotecan and topotecan in models of SCLC.

1.2.4.1 Extended Exposure of SN-38 Leads to Increased Cell Death In Vitro

Topoisomerase I inhibition has potent effects on a wide range of cancer cell lines. The activity of SN-38, the active metabolite of irinotecan, against various SCLC cell lines was investigated using in vitro growth and viability assays. Figure 1 shows that treatment with SN-38 decreased cell viability by > 90% in SCLC cell lines (DMS114, NCI-H1048). Effective cell growth inhibition was observed between 1-10 nM, with increased cell killing with increased time of exposure. The concentration range of SN-38 in which cell killing begins to occur coincides with the amount of SN-38 measured from tumor biopsies taken from patients with various solid tumors 72 hours after administration of irinotecan liposome injection (range: 3 - 163 nM; Ramanathan, 2014), which is depicted in Figure 1 as the grey shaded area. These data suggest that the prolonged duration of SN-38 TOPO1 inhibition in tumors due to irinotecan liposome injection pharmacological characteristics would be likely to result in activity in patients with SCLC.

Figure 1: Increased SN-38 Exposure Leads to Increased Cell Death In Vitro



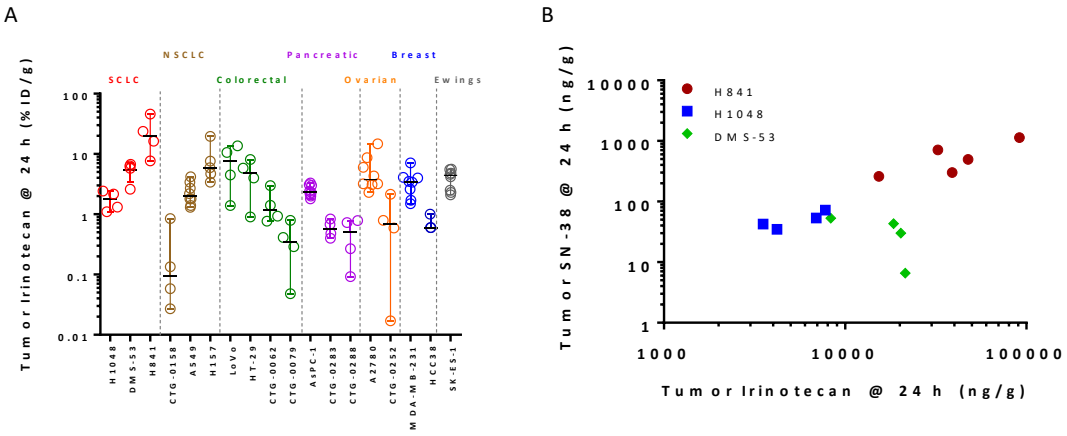
Concentration and exposure-dependent growth inhibition of SCLC cell lines by SN-38 at select time points. Range of SN-38 detected in tumor biopsies (grey box) from a previous clinical study (Ramanathan, 2014) in patients with various solid tumors is overlaid on the time-dependent SN-38 growth inhibition curves. Cell growth inhibition kinetics of SN-38 in 2 SCLC cell lines (DMS-114 and NCI-H1048) using an IncuCyte® ZOOM System over a time-course of up to 88 hours.

1.2.4.2 Irinotecan Liposome Injection Effectively Delivers Irinotecan and SN-38 to SCLC Tumors In Vivo

Liposomes require leaky vasculature to gain entry into tumor tissue. Greater than 80% of SCLC tumor lesions express detectable levels of vascular endothelial growth factor (VEGF) (Dowell, 2004). VEGF expression is involved in angiogenesis and vessel permeability that may indicate the ability to achieve effective liposome delivery into SCLC tumors. Macrophages are the primary cell type believed to phagocytose irinotecan liposome injection within the tumor tissue. While little data on macrophages in SCLC are available, macrophages have been detected in SCLC biopsy samples and ranged from few cells to heavy infiltration of the tissues (Hedbrant, 2015). Macrophages express high levels of carboxylesterase 2, which is one of the enzymes needed to convert irinotecan to its active metabolite, SN-38.

The ability of irinotecan liposome injection to deliver irinotecan and SN-38 into tumors was evaluated in SCLC cell-line derived xenograft (CDX) models (NCI-H1048, DMS-114, H841) in comparison to CDX and patient-derived xenograft models of other tumor types. Irinotecan liposome injection was administered intravenously to xenograft tumor bearing mice. At 24 hours post administration, mice were sacrificed and tumors were harvested. Irinotecan and SN-38 levels in tumors were measured by high performance liquid chromatography (HPLC). Figure 2 demonstrates that tumors derived from SCLC cell lines have similar or higher levels of irinotecan liposome injection deposition, as assessed by irinotecan content, than other tumor types. Furthermore, analysis of SN-38 levels indicates that increased irinotecan delivery was associated with increased levels of SN-38. These findings are consistent with a proposed mechanism of liposome deposition and local conversion of irinotecan to SN-38 within the tumor.

Figure 2: Irinotecan Liposome Injection-mediated Tumor Delivery of Irinotecan and SN-38 *In Vivo*

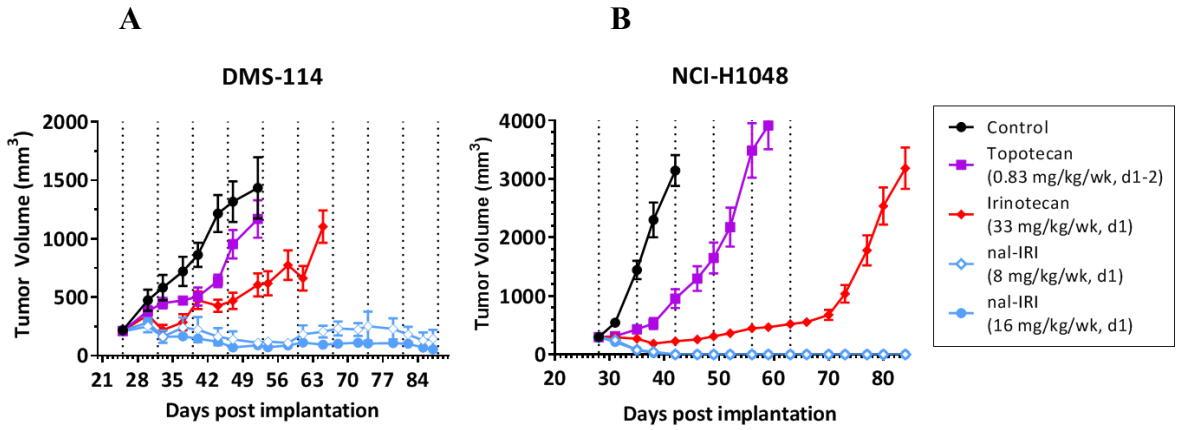


(a) Irinotecan delivered by irinotecan liposome injection was measured by HPLC at 24 h post administration in various mouse xenograft models, as shown. Data were normalized to injected dose per tumor weight. Shown here includes data obtained from SCLC CDX models. (B) Tumor irinotecan and tumor SN-38 levels, shown as ng of SN-38 per tumor weight, were measured by HPLC at 24 h post administration for three SCLC xenograft models. Increased levels of SN-38 were associated with increased levels of tumor irinotecan delivered by irinotecan liposome injection.

1.2.4.3 Irinotecan Liposome Injection Has Improved Anti-Tumor Activity as Compared to Non-liposomal Irinotecan HCl and Topotecan In Vivo

The activity of irinotecan liposome injection, non-liposomal irinotecan and topotecan were directly compared at clinically relevant doses in two CDX models. Clinically relevant doses were calculated by using standard surface area to weight ratios conversion per National Cancer Institute (NCI) guidelines. Figure 3 presents tumor growth kinetics of mice bearing SCLC xenograft tumors that were treated weekly with irinotecan liposome injection, non-liposomal irinotecan or topotecan. In both the DMS-114 and NCI-H1048 models, irinotecan liposome injection displayed significantly greater anti-tumor activity than both non-liposomal irinotecan and topotecan. Furthermore, 10 out of 10 mice treated in NCI-H1048 model treated with irinotecan liposome injection experienced complete regressions of their tumors as compared to 0 out of 10 mice treated with topotecan.

Figure 3: Anti-tumor Activity of Irinotecan Liposome Injection, Non-liposomal Irinotecan and Topotecan at Clinically Relevant Doses in DMS-114 and NCI-H1048 SCLC Xenograft Models

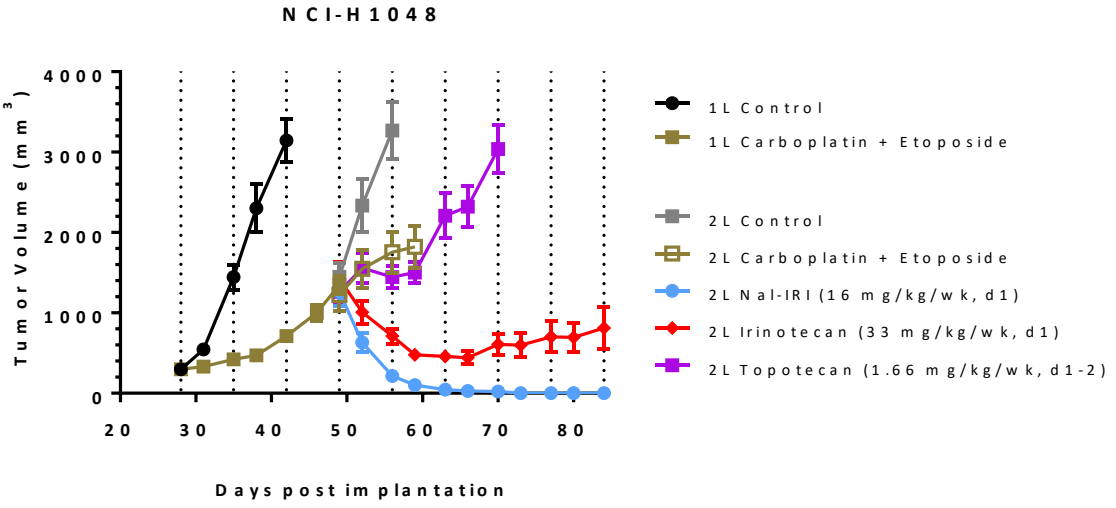


NOD/SCID mice with (A) DMS-114 or (B) NCI-H1048 SCLC xenograft tumors were treated with IV irinotecan liposome injection, IV irinotecan, IP topotecan or vehicle control. Vertical dotted lines indicate start of weekly dosing. Irinotecan liposome injection dose is shown on irinotecan HCl basis. Following treatment, irinotecan liposome injection displayed significant anti-tumor activity compared to topotecan ($p < 0.0001$ for DMS-114 on day 52 and $p < 0.0001$ for NCI-H1048 on day 59; non-parametric t-test) and irinotecan ($p < 0.0001$ for DMS-114 on day 65 and $p < 0.0001$ for NCI-H1048 on day 84; non-parametric t-test).

Note: nal-IRI = irinotecan liposome injection or liposomal irinotecan

Finally, the activity of irinotecan liposome injection, non-liposomal irinotecan and topotecan were directly compared in a second line setting of SCLC. Mice bearing NCI-H1048 SCLC tumors were treated with a carboplatin plus etoposide, a first line regimen in SCLC. Once the tumors escaped growth control by carboplatin plus etoposide, mice were randomized to either continue treatment with carboplatin plus etoposide or switch to second line treatment with either irinotecan liposome injection, non-liposomal irinotecan or topotecan. As shown in Figure 4, irinotecan liposome injection had anti-tumor activity in the second line setting and, furthermore, had significantly greater anti-tumor activity than both non-liposomal and topotecan.

Figure 4: Anti-tumor Activity of Irinotecan Liposome Injection, Non-Liposomal Irinotecan and Topotecan in a Preclinical Model of Second Line SCLC



NOD/SCID mice with NCIH1048 SCLC xenograft tumors were treated weekly with the combination of 30 mg/kg carboplatin plus 25 mg/kg etoposide. When tumor reached approximately 1200 mm^3, mice were randomized to receive weekly treatment with topotecan (1.66 mg/kg/wk administered IP in equal fractions on

days 1 and 2), non-liposomal irinotecan (33 mg/kg/wk administered IV on day 1) irinotecan liposome injection (16 mg/kg/wk administered IV on day 1), continue treatment with carboplatin plus etoposide or vehicle control. Vertical dotted lines indicate start of weekly dosing. Irinotecan liposome injection dose is shown on irinotecan HCl basis. After tumors progressed on first-line treatment with carboplatin plus etoposide, irinotecan liposome injection displayed significant anti-tumor activity compared to topotecan and irinotecan (p=0.0002 on day 70 and p=0.0002 on day 84 for topotecan and irinotecan, respectively).

Note: nal-IRI = irinotecan liposome injection or liposomal irinotecan

1.3 Irinotecan Liposome Injection Clinical Experience

Irinotecan liposome injection has been studied in patients with solid tumors, including cervical cancer, gastric cancer, pancreatic cancer, and colorectal cancer. Irinotecan liposome injection under the tradename ONIVYDE®, was approved in the United States and Taiwan in 2015 and in the EU and Australia in 2016 and in Canada, Switzerland, and South Korea in 2017 in combination with 5-FU and LV, for the treatment of patients with metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy. The registration for this indication is under review in several other countries. Disease areas currently being studied include front-line pancreatic cancer, glioma, breast cancer and several pediatric solid tumors, including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, and osteosarcoma. Details of completed and ongoing studies are presented in the Investigator's Brochure (IB).

1.3.1 United States Food and Drug Administration Approval of ONIVYDE® and Determination of Irinotecan Liposome Injection Strength

ONIVYDE® (irinotecan liposome injection, liposomal irinotecan, or nal-IRI) is formulated with irinotecan hydrochloride trihydrate into a liposomal dispersion for intravenous use.

ONIVYDE® in combination with 5-FU/LV was approved by the US Food and Drug Administration (FDA) in October 2015 for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. Prior to FDA approval of ONIVYDE®, the compound was identified as MM-398 (or PEP02), and MM-398 dosing has been expressed on the basis of irinotecan hydrochloride trihydrate salt. At the time of approval, the FDA applied the USP Salt Policy; therefore, the drug strength of ONIVYDE® in the United States is now expressed in terms of the active moiety rather than the salt.

Converting ONIVYDE® dose from irinotecan hydrochloride trihydrate salt base (as traditionally has been described for MM-398 until the US approval) to a dose based on irinotecan free base is accomplished by substituting the molecular weight of irinotecan hydrochloride trihydrate (677.19 g/mole) with the molecular weight of irinotecan free base (586.68 g/mole), which results in a conversion factor of 0.866. Therefore, the 80 mg/m^2 based on irinotecan hydrochloride trihydrate salt is equivalent to a 69.3 mg/m^2 based on irinotecan free base. This value was rounded to 70 mg/m^2 in the United States Product Information to minimize any potential dosing errors.

ONIVYDE® was approved by the European Medicines Agency (EMA) in October 2016 for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU/LV, in adult patients who have progressed following gemcitabine based therapy. As approved in the EU, ONIVYDE® dosing strength is expressed on the basis of irinotecan hydrochloride trihydrate salt. Therefore, the dose of ONIVYDE® described in the Summary of Product Characteristics (SmPC) is 80 mg/m^2 based on irinotecan hydrochloride trihydrate salt (versus 70 mg/m^2 when expressed on irinotecan free base).

For the purpose of this protocol, all applicable ONIVYDE® (irinotecan liposome injection or liposomal irinotecan or nal-IRI) dose regimens, descriptions and modifications are based on the irinotecan free base.

1.3.2 Clinical Pharmacology

1.3.2.1 Association Between Exposure and Efficacy with Irinotecan Liposome Injection

Population PK analysis of data from the irinotecan liposome injection + 5-FU/LV arm in the NAPOLI-1 trial (patients with advanced metastatic pancreatic cancer) (Adiwijaya et al, 2016) was suggestive of a relationship between exposure and efficacy. In the irinotecan liposome injection+5-FU/LV arm of NAPOLI-1, longer OS and PFS were associated with longer time of exposure of un-encapsulated SN-38, the active metabolite of irinotecan, above a threshold (>0.03 ng/mL) and with higher AUC of un-encapsulated SN-38. Longer duration of exposure of un-encapsulated SN-38 above 0.03 ng/mL was associated with a higher probability of achieving an objective response in the irinotecan liposome injection+5-FU/LV arm.

1.3.2.2 Association between Exposure and Safety with Irinotecan Liposome Injection

The exposure-safety relationship for irinotecan liposome injection is based on population PK analysis of data from 353 patients (Adiwijaya et al, 2016). Higher total irinotecan maximum serum concentration (C_{max}) was associated with higher probability of observing Grade 3 or higher diarrhea. Higher C_{max} of un-encapsulated SN-38 was associated with higher probability of both incidence and severity of neutropenia treatment-emergent adverse events (TEAEs), with different probabilities of observing Grade 3 or higher neutropenia with and without co-administration with 5-FU/LV.

1.3.3 Clinical Data Supporting Evaluation of Dose

1.3.3.1 Clinical Data Supporting Evaluation of 85 mg/m^2 Every 2 Weeks

The maximum tolerated dose of irinotecan liposome injection in a Phase 1 study was established to be 104 mg/m^2 (dose expressed as free base) administered every three weeks.

The safety of irinotecan liposome injection monotherapy given every 2 weeks was evaluated in an open-label phase I dose finding study conducted in Taiwanese patients with colorectal cancer "Phase I and Pharmacokinetic Study of Biweekly PEP02 (Liposome Irinotecan) in Patients with Metastatic Colorectal Cancer Refractory to First-line Oxaliplatin-based Chemotherapy (PIST-CRC-01)".

The starting dose level was 69 mg/m^2 and escalated to 77 and then to 86 mg/m^2 (doses expressed as irinotecan free base).

Eighteen patients were enrolled at the dose levels of 69, 77 and 86 mg/m^2 of irinotecan liposome injection (doses expressed as irinotecan free base) with 6 patients at each dose level. Of the total of 18 patients, the average age was 58.6 years old; 9 (50%) patients were female and 9 (50%) patients were male. The average weight at screening was 61.8 kg. Twelve (66.7%) and 6 (33.3%) patients had an ECOG 0 and 1 performance status, respectively. All patients had received prior oxaliplatin-based treatment for their metastatic colorectal cancer. All patients were Chinese.

A total of 109 cycles of treatment (2 weeks per cycle in this study) were administered, with a mean of 6 cycles per patient (range 2-18, median 4 cycles/patient). There was 1 DLT at each dose level (Grade 3 neutropenia with infection and Grade 3 diarrhea).

The most commonly reported TEAEs occurring in >20% of patients were diarrhea, decreased appetite, and alopecia (each in 16 patients, 88.9%); anemia and nausea (each in 14 patients, 77.8%); vomiting (13 patients, 72.2%); mucosal inflammation (12 patients, 66.7%);

leukopenia, constipation (each in 11 patients, 61.1%); neutropenia (10 patients, 55.6%), fatigue (9 patients, 50.0%); alkaline phosphatase increased, hypokalemia (each in 8 patients, 44.4%); dizziness (7 patients, 38.9%); abdominal distension, pain (each in 6 patients, 33.3%); abdominal pain, urinary tract infection, gamma-glutamyl transferase increased, insomnia, skin hyperpigmentation (each in 5 patients, 27.8%); abdominal pain upper, influenza like illness, aspartate aminotransferase (AST) increased, weight decreased, cholinergic syndrome, cough (each in 4 patients, 22.2%). Overall, 13 patients (72.2%) experienced at least one (TEAE) of Grade 3 or higher severity. The most common Grade 3 or TEAEs were vomiting (5 patients, 27.8%) and diarrhea and nausea (each in 3 patients, 16.7%).

In terms of efficacy, there were 4 partial responses (22%), two in the 69 mg/m^2 (dose expressed as irinotecan free base) cohort, and 1 in each of the other two cohorts.

In conclusion, irinotecan liposome injection 69 – 86 mg/m^2 (doses expressed as irinotecan free base, corresponding to 80-100 mg/m^2 irinotecan liposome injection strength expressed as irinotecan hydrochloride) given every two weeks appeared generally well tolerated and active when administered as a single agent in patients with advanced colorectal carcinoma refractory to first line oxaliplatin-based regimens.

1.3.3.2 Clinical Data to Justify 70 mg/m^2 Every 2 Weeks in Part 2

Based on the safety and tolerability of irinotecan liposome injection monotherapy observed at the two different dose levels of 85 mg/m^2 and 70 mg/m^2 (free base equivalent) in Part 1, the recommended dose was determined to be 70 mg/m^2 administered every two weeks.

The assessment of the available safety and efficacy data from Part 1 is presented in detail in the IB. Thirty patients were treated for more than 12 weeks in Part 1.

Five patients received irinotecan liposome injection at 85 mg/m^2 on a bi-weekly basis. This dose was deemed not tolerable due to DLT (defined in Section 3.1.1). Once the first two DLT events were reported in two patients in the 85 mg/m^2 treatment group, enrollment at 85 mg/m^2 dose level was stopped and dose reduction to 70 mg/m^2 was recommended for patients who continued to receive treatment in the 85 mg/m^2 treatment group, (total of five patients), and the 70 mg/m^2 treatment group was initiated.

As presented in the IB at an interim data cut-off of 08 May 2019, 25 patients received irinotecan liposome injection at 70 mg/m^2 on a biweekly basis. The 70 mg/m^2 dose was deemed tolerable: 40% of patients at the 70 mg/m^2 dose level experienced Grade 3 or higher treatment-related TEAEs. Diarrhea was the most common gastrointestinal adverse event.

Preliminary efficacy at 70 mg/m^2 dose level identified 11 patients with partial responses (ORR 44%). Best overall response BOR (partial response +stable disease) was 72%.

Part 1 demonstrated encouraging anti-tumor activity of irinotecan liposome injection at 70 mg/m^2 in patients with SCLC (ORR: 44%, BOR: 72%). Irinotecan liposome injection at 70 mg/m^2 was generally well tolerated.

*1.3.4 Clinical Data in UGT1A1*28 Homozygous Patients*

Human uridine diphosphate glucuronosyl transferase (UGT) 1A1 is the enzyme that detoxifies neurotoxic bilirubin by conjugating it with glucuronic acid and plays a critical role in the detoxification and excretion of endogenous and exogenous lipophilic compounds mainly in the liver and gastrointestinal tract. UGT1A1 is responsible for the glucuronidation of SN-38 to SN-38G as part of the mechanism of SN-38 clearance. UGT1A1*28 7/7 homozygosity results in reduced UGT enzymatic activity and may result in elevated SN-38 levels and thereby contribute to increased SN-38 mediated toxicity following treatment with Camptosar® (non-liposomal irinotecan) (Camptosar® USPI 2019).

Multiple studies have evaluated the association between UGT1A1*28 homozygosity, SN-38 concentration, and safety in patients treated with non-liposomal irinotecan and suggest the associations are dose and inter-patient variability dependent. Higher increase in SN-38 concentrations were observed for UGT1A1 *1/*28 (6/7) (heterozygous) and UGT1A1 *28/*28 (7/7) (homozygous) genotypes compared to UGT1A1 *1/*1 (6/6) (wild type) genotype when non-liposomal irinotecan was administered at a high dose of 300 mg/m^2 (Iyer 2002) than when it was administered at a low dose of 20 mg/m^2 (Stewart 2007). Although absolute neutrophil count (ANC) nadirs significantly correlated with SN-38 exposure at the higher dose of 300 mg/m^2 of non-liposomal irinotecan, the difference between the severe grades of neutropenia (Grade 3 higher or above) were not found to be statistically significant amongst the three genotypes (Iyer 2002). Evaluation of lower dosing regimens of non-liposomal irinotecan (15 to 75 mg/m^2 daily for 5 days for 2 weeks) found that despite the increase of SN-38 concentrations observed, UGT1A1 genotype was not a significant single predictor for irinotecan toxicity. In a study of 66 patients who received single-agent non-liposomal irinotecan (350 mg/m^2 every 3 weeks), the incidence of Grade 4 neutropenia in patients heterozygous for UGT1A1*28 (6/7) and homozygous (7/7) for the UGT1A1*28 was 12.5% and up to 50% respectively (Camptosar® USPI 2019). In a subsequent study, association between UGT1A1*28 homozygosity and hematological toxicity was observed only in patients treated with >150 mg/m^2 non-liposomal irinotecan. By contrast, at lower dose of non-liposomal irinotecan (100 to 125 mg/m^2 every week) similar hematological toxicities were observed for both UGT1A1*28/*28 and those with a UGT1A1*1/*28 or UGT1A1*1/*1 (Hoskins 2007). Publications from prospective trials of 250 metastatic colorectal cancer patients studying the FOLFIRI regimen (irinotecan dose of 180 mg/m^2) and the role of UGT1A1*28 polymorphism in toxicity and efficacy did not support a dose reduction in patients with UGT1A1*28 homozygosity and further suggest that the data are insufficient for recommending specific dose adjustments based on the UGT1A1 genotype (Toffoli 2006). More recently, a study in 2982 patients with colorectal cancer from trial PETACC-3, found that a complex set of risk factors is involved in the development of toxicity, including UGT1A1. However, other parameters that are readily available in clinical practice, notably sex, age and performance score, were stronger predictors than the UGT1A1*28 genotype (Tejpar 2018).

In patients treated with irinotecan liposome injection, the association between UGT1A1*28 (7/7) homozygosity, SN-38, and hematologic toxicity is primarily obtained from the NAPOLI-1 study, where UGT1A1*28 homozygous patients were treated at a reduced dose (50 mg/m^2 versus 70 mg/m^2 (FBE) every 2 weeks in combination with 5-FU/LV, or 70 mg/m^2 versus 100 mg/m^2 (FBE) every 3 weeks monotherapy). The NAPOLI-1 study Population PK results concluded that no significant association was observed between UGT1A1*28 homozygosity and SN-38 exposure. In addition, the UGT1A1*28 homozygous Caucasian patients were predicted to have an approximately 2% higher incidence of neutropenia Grade 3 or higher TEAEs compared to nonhomozygous Caucasian patients. An additional pooled Population PK study showed that overall exposure to SN-38 was deemed similar between Japanese and non-Japanese populations with unrecognisable influence of UGT1A1 genotype. Based on these data, patients homozygous for UGT1A1*28, administered with the same dose of irinotecan liposome injection administration as non-homozygous patients, do not appear to be at significant clinical risk of increased Grade 3 or higher neutropenia.

Mechanistically, these data indicate that the association of UGT1A1*28 polymorphism to SN-38 concentration and to hematological toxicity appear to depend on the incoming load of SN-38 to be metabolized by UGT enzymes. The dose-dependent association of UGT1A1*28 and SN-38 or neutropenia observed with Camptosar® administration is consistent with this hypothesis. Furthermore, liposomal encapsulation appears to spread out the incoming load of

SN-38 by controlling the release of irinotecan. This is supported by a study in patients with advanced gastric cancer in which 100 mg/m^2 irinotecan liposome injection administration resulted in five times lower plasma SN-38 C_{max} as compared to 300 mg/m^2 non-liposomal irinotecan (PEP0206) (Roy, 2013). Reduced load of SN-38 may allow for metabolism by UGT enzymes even in patients with reduced UGT enzyme activities (for example, UGT1A1*28 homozygous patients).

Despite the lack of associations between UGT1A1*28 homozygosity, safety, and PK, the irinotecan liposome injection US package insert followed the NAPOLI-1 protocol that started homozygous patients at a lower dose due to the comparatively small number of patients with UGT1A1*28 homozygous treated with irinotecan liposome injection. Therefore, the absence of a relationship between UGT1A1*28 homozygosity and increased SN-38 exposure or toxicity following irinotecan liposome injection administration warrants further study.

In this study, the starting dose of irinotecan liposome injection will be the same regardless of UGT1A1*28 genotype. UGT1A1*28 genotype will be collected on all patients as a safety biomarker to further analyze the association between UGT1A1*28 homozygosity, SN-38 concentration and toxicity. Irinotecan liposome injection dose reduction will follow the same dose reduction rules for all patients regardless of UGT1A1*28 genotype. Patients with UGT1A1*28 homozygosity will be closely monitored for safety in comparison to the safety in patients with UGT1A1*28 non-homozygous status by the Medical Monitors of the Sponsor and by the DMC.

2 OBJECTIVES

This study will be conducted in two parts: an open-label, single-arm, safety run-in (Part 1) to confirm the Part 2 dose of irinotecan liposome injection, followed by a randomized, open-label comparison of irinotecan liposome injection and topotecan in patients with SCLC.

2.1 Part 1

2.1.1 Primary Objectives

The primary objectives of Part 1 are:

- Describe the safety and tolerability of irinotecan liposome injection monotherapy administered every 2 weeks
- To determine the irinotecan liposome injection monotherapy dose (85 mg/m^2 or 70 mg/m^2 administered every 2 weeks) for Part 2 of this study.

2.1.2 Secondary Objectives

The secondary objectives of Part 1 are to assess the preliminary efficacy of irinotecan liposome injection (at **either** the 85 mg/m^2 dose level **or** the 70 mg/m^2 dose level) as determined by:

- Objective response rate (ORR)
- Progression free survival (PFS)
- Overall survival (OS).

2.1.3 Exploratory Objectives

- To describe QTcF following treatment with irinotecan liposome injection.
- To explore the biomarkers associated with toxicity and efficacy following treatment with irinotecan liposome injection in this patient population.
- To describe the association between UGT1A1*28 and other UGT1A1 genotypes, SN-38 concentration and safety.

- To evaluate the pharmacokinetics and the relationship between pharmacokinetic exposure and efficacy and safety following irinotecan liposome injection in this patient population.
- To explore patient-reported outcomes (PROs) using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC-QLQ-LC13), Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C), and EuroQol 5-dimension health status questionnaire (5 level) (EQ-5D-5L).

2.2 Part 2

2.2.1 Primary Objective

The primary objective of Part 2 is to compare overall survival following treatment with irinotecan liposome injection with overall survival following treatment with intravenous (IV) topotecan.

2.2.2 Secondary Objectives

The secondary objectives of Part 2 are to compare the following between the treatment arms:

- Progression free survival (PFS)
- Overall response rate (ORR)
- Patient reported outcomes (PRO)
- Safety profile.

2.2.3 Exploratory Objectives

The exploratory objectives include:

- To explore the biomarkers associated with toxicity and efficacy following treatment with irinotecan liposome injection in this patient population.
- To describe the association between UGT1A1*28 and other UGT1A1 genotypes, SN-38 concentration (irinotecan liposome injection treated patients only) and safety.
- To evaluate the pharmacokinetics and the relationship between pharmacokinetic exposure and efficacy and safety following irinotecan liposome injection in this patient population.
- To compare the rate of development/time to development of central nervous system (CNS) progression and development of new CNS metastases.
- To compare time to treatment failure (TTF) between treatment arms.
- To assess the proportion of patients with improvement in symptoms as measured by EORTC QLQ-C30/LC13 dyspnea scale
- To assess the proportion of patients with improvement in symptoms as measured by the EORTC QLQ-LC13 cough scale
- To compare the effect of irinotecan liposome injection vs. topotecan on symptoms (other than dyspnea and cough), functioning and global health status as measured by EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L.

3 STUDY DESIGN

3.1 Overview of Study Design

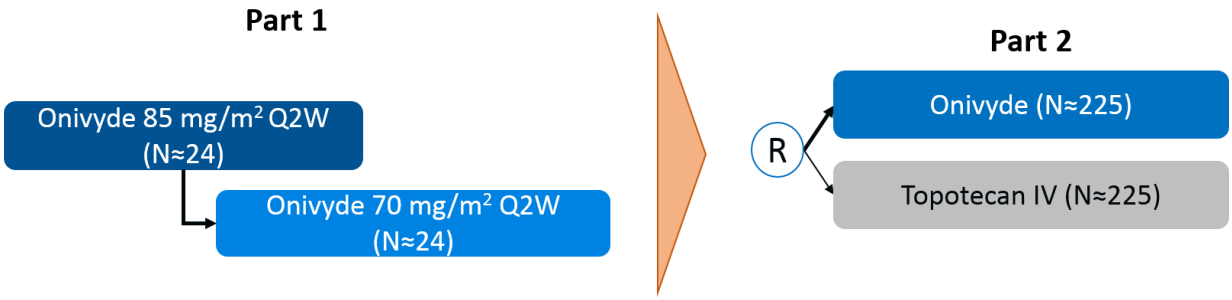
This study will be conducted in two parts: an open-label, single-arm, safety run-in period (Part 1) followed by a randomized period (Part 2) assessing irinotecan liposome injection versus

IV topotecan in patients with SCLC who have progressed on or after platinum-based first line therapy (see Figure 5).

Part 1 is an open-label, single-arm, safety run-in evaluation of irinotecan liposome injection administered every 2 weeks, intended to confirm the anticipated Part 2 regimen (85 mg/m^2), based on safety and preliminary efficacy. A contingency has been included for evaluation of irinotecan liposome injection at a dose level of 70 mg/m^2, should the higher dose level of 85 mg/m^2 result in unacceptable toxicity.

Part 2 will be randomized, and assess the efficacy of irinotecan liposome injection versus IV topotecan.

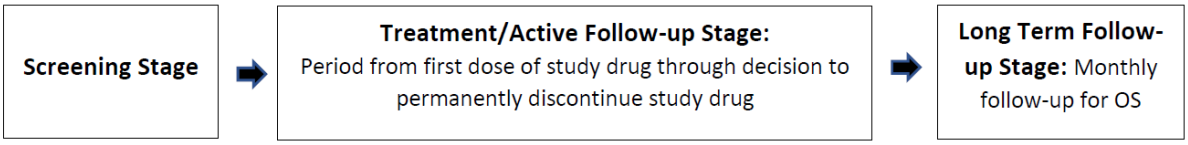
Figure 5: Study Schema



Note: ONIVYDE is also known as irinotecan liposome injection, liposomal irinotecan or nal-IRI.

Each part will consist of three stages: screening stage, treatment/active follow-up stage and long-term follow-up stage. Once consented, patients will enter a screening stage. Upon first dose of study treatment in Part 1 or randomization (Part 2), patients will enter the treatment/active follow-up stage. Once a decision is made to permanently discontinue the patient from study treatment, a 30-day follow-up visit will occur and the patient will enter the long-term follow-up stage. The stages for this trial are outlined in the schematic below.

Figure 6: Description of Treatment Stages



It is intended that all patients in Parts 1 and 2 will be treated until progressive disease or unacceptable toxicity. Patients may take a treatment holiday and resume study treatment under certain instances. Detailed rule for pausing and resuming study treatment can be found in Section 6.2.1. Cross-over between treatment arms is not permitted.

Upon permanent discontinuation of study treatment (defined as patients with progressive disease whilst receiving study treatment and/or those assessed by the Investigator as unable to continue or resume study treatment due to unacceptable toxicity), patients will return to the study site for a 30-day follow-up visit. After this visit, patients will continue to be followed for OS status by phone, email or a visit to the study site once every month until death or study closure, whichever occurs first.

3.1.1 Part 1

Part 1 is an open-label, single-arm, safety run-in evaluation of irinotecan liposome injection administered every 2 weeks, intended to confirm the anticipated Part 2 regimen (85 mg/m^2), based on safety and preliminary efficacy. A contingency has been included for evaluation of

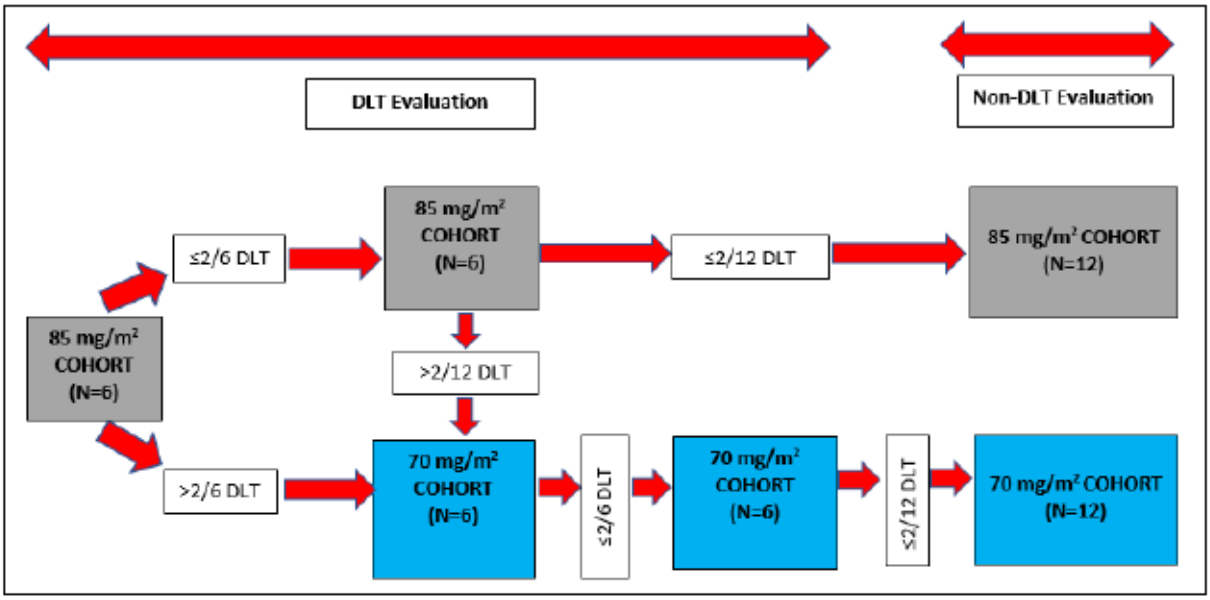
irinotecan liposome injection at a dose level of 70 mg/m^2, should the higher dose level of 85 mg/m^2 result in unacceptable toxicity. At either dose level of irinotecan liposome injection up to 24 patients will be enrolled.

A quality of life assessment will be performed using the EORTC-QLQ-C30, EORTC-QLQ-LC13, PGI-S, PGI-C and the EQ-5D-5L in Part 1. All patient-report instruments will be administered at screening and prior to dosing at 6-week intervals (prior to any other assessment procedure) following start of treatment, at treatment discontinuation and at the 30-day follow-up visit. The PGI-C is not included in the screening assessment.

The safety assessment and the corresponding rule of expansion will be conducted according to a "6+6" design followed by enrollment of an additional 12 patients (as described below). Patients will initially be treated with irinotecan liposome injection 85 mg/m^2 every 2 weeks. Dose limiting toxicities will be evaluated for the first 12 patients treated during the first 28 days of treatment (or up to 14 days after the second dose of study treatment if there is a treatment delay due to non-DLT related reasons).

- Among the first 6 patients receiving irinotecan liposome injection 85 mg/m^2, (i.e. 85 mg/m^2 cohort) if ≤2 patients experience a DLT, another 6 patients will be enrolled. Otherwise, enrollment into the 70 mg/m^2 cohort will be initiated.
- Among the first 12 patients receiving irinotecan liposome injection 85 mg/m^2, if ≤2 patients experience a DLT, this cohort will be expanded by 12 additional patients. Otherwise, the enrollment of the 85 mg/m^2 cohort will be stopped and the enrollment of the 70 mg/m^2 cohort will be initiated.

Figure 7: Treatment Cohorts: Safety Run-in



If the 70 mg/m^2 cohort is enrolled, the same "6+6" design followed by enrollment of an additional 12 patients, and the same DLT guidelines will be used as that for the 85 mg/m^2 cohort. If ≤2 patients among the first 12 patient receiving irinotecan liposome injection 70 mg/m^2 experience a DLT, then that dose level will be declared tolerable and this cohort will be expanded by 12 additional patients. Otherwise, additional dose reduction(s) may be considered.

NOTE that in either the 85 mg/m^2 cohort or the 70 mg/m^2 cohort, there will be no stopping rules based on the DLT assessment; however, DLTs will continue to be assessed among the additional 12 patients recruited after the first 12 patients have completed DLT evaluation.

The decision of which dose to use for Part 2 will be made based on the totality of data from all patients treated in Part 1.

If a decision is made to terminate the irinotecan liposome injection 85 mg/m^2 dose level cohort (and instead initiate enrollment into the 70 mg/m^2 cohort) patients who are tolerating the 85 mg/m^2 dose level will remain at that dose level (unless subsequent toxicity requires a dose modification).

During the DLT evaluation period in either the 85 mg/m^2 or 70 mg/m^2 cohort, the following adverse events (AEs) should be considered as DLTs if they occur during the first 28 days of treatment (or 14 days after the 2nd dose of study treatment if there is a treatment delay according to Section 6.2) and are deemed related to the study treatment by the Investigator:

- Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal supportive therapy
- Inability to resume subsequent treatment within 14 days of the scheduled date, due to drug-related toxicity
- Grade 3-4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or by infection
- Any Grade 4 non-hematologic toxicity with the exception of the following:
  - Fatigue/asthenia lasting < 14 days
  - Nausea and vomiting lasting ≤ 72 hours duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic treatment)
  - Diarrhea ≤ 72 hours duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)
- Grade 3 non-hematologic toxicity with the exception of the following:
  - Any gastrointestinal disorder and dehydration (with associated signs and symptoms) unless Grade 3 toxicity persists despite optimal medical management for > 72 hours
  - Pain unless Grade 3 toxicity persists despite optimal medical management
  - Fatigue, fever, flu like symptoms, infections and infestations
  - Infusion reaction (and associated symptoms) unless it occurs following steroid premedication
  - Hepatic and kidney function abnormalities, and electrolyte abnormalities unless they persist, despite optimal medical management.

The determination of whether an AE is considered a DLT will be made by the safety review committee (i.e. the Part 1 Investigators and the Medical Monitor(s) of the Sponsor). Other AEs, not meeting the DLT criteria above, that are deemed related to study treatment can also be considered a DLT event at the discretion of the safety review committee. Safety review meetings between investigators and sponsor will occur regularly during Part 1 of the study with at least monthly meetings, or more frequently, if required.

The decision on Part 2 dose level, as per Part 1 outcome, will be communicated to all participating investigators prior to initiating Part 2 recruitment.

3.1.2 Part 2

Approximately 450 eligible patients will be randomized in a 1:1 ratio between the experimental arm (Arm A: based on the findings of Part 1 [either 85 mg/m^2 or 70 mg/m^2 of irinotecan liposome injection]) and the control arm (Arm B: IV topotecan). Note that following assessment of the available safety and efficacy data from Part 1 the 70 mg/m^2 dose was chosen for Arm A (see Section 1.3.3.2). Patients will be randomized to the treatment arms using an Interactive Response Technology System (IRT) at a central location. Randomization will be stratified, based on the following factors:

- Region (North America vs. Asia vs Other)
- Platinum sensitivity (sensitive vs. resistant)
- Performance status (ECOG 0 vs. 1)
- Prior immunotherapy (yes vs. no)

(Note: for platinum sensitivity, progression within 90 days from the completion of first-line platinum therapy is considered "platinum resistant" and the others "platinum sensitive". Prior immunotherapy sensitivity should not be confused with platinum sensitivity).

Only region (North America vs. Asia vs. Other) and platinum sensitive vs. resistant will be used for the stratified efficacy analysis.

Tumor assessments will be performed every 6 weeks (± 1 week), using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines Version 1.1 (Parts 1 and 2) and Response Assessment in Neuro-oncology Brain Metastases (RANO-BM) criteria for CNS lesions (Part 2). Tumor assessment at screening and for all subsequent visits will be computed tomography (CT) with contrast (chest/abdomen required and pelvis [or other areas] if clinically indicated) and brain magnetic resonance imaging (MRI) with contrast. For patients who are allergic to IV contrast or cannot tolerate IV contrast due to impaired renal function or other issues, a non-enhanced CT or MRI is acceptable. Each follow-up tumor assessment should use the same assessment method as performed at screening, unless medically contraindicated. All patients will have imaging of the brain at screening and at each assessment. Patients who discontinue study treatment, for reasons other than disease progression per RECIST Version 1.1 or RANO-BM criteria (for CNS lesions, Part 2) should continue to be followed with the same schedule of tumor assessments (every 6 weeks ± 1 week) until radiological documentation of progressive disease.

Progressive disease will be determined by local radiology review and/or by investigator assessment, to ensure optimal and timely medical management. The Sponsor will collect and store all tumor assessment images on all patients throughout the study. An independent central review of the scans will be performed at the discretion of the Sponsor to support potential early filing to regulatory authorities. All patients will be followed at least monthly for survival status until death, loss to follow-up or study closure, whichever comes first.

A quality of life assessment will be performed using the EORTC-QLQ-C30, EORTC-QLQ-LC13, PGI-C, PGI-S, and the EQ-5D-5L in Part 2. Although the PGI-C and PGI-S are not specified as exploratory objectives in Part 2, they will serve as anchors for deriving a within-patient meaningful change threshold in Part 2. All patient-reported outcome (PRO) instruments will be administered at screening and prior to dosing at 6-week intervals (and prior to any other assessment procedures) following start of treatment, at treatment discontinuation and at the 30-day follow-up visit. Patients who discontinue study treatment, for reasons other than disease progression, should continue to complete all QoL assessments every 6 weeks until radiological documentation of progressive disease or until the start of alternative anti-neoplastic therapy. The PGI-C is not included in the screening assessment. Adverse events

will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For summary of AEs, events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 21.0 or later) at the start of the study.

The primary analysis is planned when at least 350 OS events have occurred in Part 2. An interim analysis of OS for futility is planned at approximately 29% information time, after at least 100 OS events have occurred. At the time of the interim analysis, ORR by blinded independent central review (BICR) tumor assessments will be analyzed descriptively by the independent DMC for the first 200 patients randomized in Part 2 of the study (i.e. approximately 100 patients from each arm). The independent DMC will notify the Sponsor if pre-specified criteria for ORR are met, as detailed in the DMC charter. A supplemental interim analysis is planned on data collected 24 weeks after the last patient has been randomized based on the ITT Population. Details of the ORR by BICR analysis are provided in the section on statistical methods and in the Statistical Analysis Plan (SAP).

Pharmacokinetics

Sparse plasma samples for PK of irinotecan liposome injection and SN-38 will be collected from all patients receiving irinotecan liposome injection (Part 1 and Part 2).

Biomarker Exploratory Endpoint and Evaluation

The exploratory endpoint comprises biobanking of samples for future analyses, among patients who consent for optional exploratory biomarker analysis. Analysis of biobank samples will be performed outside the scope of the main study and will be reported separately. Biobank samples may be stored for up to 15 years.

Archival tumor tissue samples will be collected at baseline (C1D1), if available.

Blood and stool samples will be collected as follows in both the ONIVYDE® and Topotecan arms:

- At baseline (C1D1)
- At week 6 (C2D1)
- Treatment pause or Week 12 (C3D1) or end of treatment (whichever occurs first).

3.2 Study Duration and Study Closure

Upon completion of screening (up to 28 days) all patients in Parts 1 and 2 will be treated until progressive disease or unacceptable toxicity. Each patient's participation in the study treatment phase will end at the time of their 30-day follow-up assessment. Then, each patient will enter the long-term follow-up when they should continue to be followed for survival status via telephone, email, clinic visit, or medical record review until death, lost to follow-up, withdrawal of consent or study closure, whichever occurs first as described in Section 6.4

The overall duration of the entire study is anticipated to be approximately 5 years. The study will be considered to have started when the first patient has provided signed informed consent and to have ended once all patients are off study treatment and at least 350 OS events have occurred in randomized patients.

3.3 Safety Review Committee and Independent Data Monitoring Committee

Safety Review Committee

A Safety Review Committee (SRC) (comprising the Part 1 Investigators and the Medical Monitor(s) of the Sponsor) will be responsible for supervising review of DLT and other safety data during Part 1 and the decision whether or not to implement enrollment into an irinotecan liposome injection 70 mg/m^2 cohort.

The final decision to proceed to Part 2 (and the dose level of irinotecan liposome injection), will be made by the Sponsor in consultation with the study steering committee, after consideration of all available efficacy and safety data from Part 1 of the study.

Independent Data Monitoring Committee

An independent DMC will be established to monitor data in Part 2 of the study, to evaluate the planned interim analysis and to make recommendation to the Sponsor based on the results of the interim analysis over continuation or stoppage of the study. During the course of the study, regular review of safety data will be conducted in accordance with the DMC charter. The first safety review by the DMC will take place after the 30th patient is randomized and treated for at least one cycle or permanently discontinues study drug, whichever occurs first. The timing and details of subsequent data reviews will be detailed in the DMC charter. Items reviewed will include (but not limited to) safety events, results of interim analysis, any available results of PK testing and UGT1A1*28 genotype. Attention will be paid to determining whether any study procedure needs to be modified for patients who are homozygous for UGT1A1*28.

4 STUDY POPULATION

4.1 Inclusion Criteria

To participate in the study patients must meet the following inclusion criteria, and none of the exclusion criteria:

General Inclusion Criteria

(1) At least 18 years of age.

(2) Able to understand and provide the study informed consent.

(3) ECOG performance status of 0 or 1.

(4) Life expectancy >12 weeks.

Disease Specific Inclusion Criteria

(5) Histopathologically or cytologically confirmed small cell lung cancer according to the International Association for the Study of Lung Cancer (IASLC) histopathological classification. Mixed or combined subtypes according to the IASLC are not allowed.

(6) Evaluable disease as defined by RECIST Version 1.1 guidelines (patients with non-measurable lesions are eligible).

(7) Radiologically confirmed progression on or after first-line platinum based chemotherapy (carboplatin or cisplatin), or chemo-radiation including platinum-based chemotherapy for treatment of limited or extensive stage SCLC. In addition to platinum-based regimen, one line of immunotherapy as monotherapy or in combination, in first or in second line setting is allowed.

(8) Recovered from the effects of any prior chemotherapy, surgery, radiotherapy or other anti-neoplastic therapy (recovered to Grade 1 or better, with the exception of alopecia, peripheral neuropathy, or ototoxicity).

Hematologic, Biochemical and Organ Function Inclusion Criteria

(9) During the Screening period, adequate bone marrow reserves as evidenced by:

- (a) Absolute neutrophil count >1,500 cells/µL (1.5 x 10^9/L) without the use of hematopoietic growth factors within the immediately preceding 14 days;
- (b) Platelet count >100,000 cells/µL (100 x 10^9/L);
- (c) Hemoglobin >9 g/dL; transfusions are allowed

(10) Adequate hepatic function as evidenced by:

(a) Serum total bilirubin within normal range for the institution

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

(c) Serum albumin ≥3.0 g/dL (≥30 g/L)

(11) Adequate renal function as evidenced by a serum creatinine ≤1.5 x ULN and creatinine clearance ≥40 mL/min. Actual body weight should be used for calculating creatinine clearance using the Cockcroft-Gault Equation (except for patients with body mass index >30 kg/m^2 when lean body weight should be used instead):

$$\text{Serum Creatinine (mg/min)} = \frac{(140 - \text{Age (years)}) \times (\text{Weight (kg)})}{72 \times \text{Serum Creatinine (mg/dL)}} \times \text{Sex}$$

where Sex = 1 for male and 0.85 for females

(12) Electrocardiogram (ECG) without any clinically significant findings at screening, as per investigator's assessment.

Additional Disease Specific Inclusion Criteria

(13a) Patients with certain types of asymptomatic CNS metastases that meet ALL the following criteria are eligible.

a) Patients with asymptomatic CNS metastases prior to enrollment

b) Prior radiation for CNS metastatic disease is completed ≥4 weeks prior to enrollment

c) CNS metastases that are stable or have decreased according to the post radiation follow-up scan that is conducted at least 4 weeks after completion of radiation treatment for CNS lesion.

d) Patients have discontinued corticosteroids or are on stable low-dose steroids (prednisone or equivalent 10 mg daily or less) for at least 1 week after completion of radiation for CNS lesion prior to enrollment.

4.2 Exclusion Criteria

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

General Exclusion Criteria

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

(2) Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on a serum pregnancy test. Females of childbearing potential are defined as fertile, following menarche and until becoming postmenopausal unless permanently sterile. Postmenopausal women are defined as those that have an absence of menstruation for at least 2 years. If necessary, follicle stimulating hormone results >50 IU/L at screening are confirmatory in the absence of a clear postmenopausal history. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Male patients must agree to use condoms during the study and for 4 months following the last dose of study drug. Female patients of reproductive potential must agree to use a

highly effective method of birth control, during the study and for 1 month following the last dose of study drug.

Disease Specific Exclusion Criteria

(3) Patients with large cell neuroendocrine lung carcinoma.

(4) Patients who have received any of the following treatments:

(a) Prior treatment regimens with irinotecan, topotecan or any other TOP I inhibitor including investigational TOP I inhibitors;

(b) Retreatment with platinum-based regimen after relapse of first-line platinum-containing therapy;

(c) Any antibody-drug conjugates or molecular targeted agents (e.g. poly ADP-ribose polymerase inhibitors), either alone or in combination with other treatments;

(d) More than one line of prior immunotherapy;

(e) Any other additional regimen of prior cytotoxic chemotherapy, not described above.

(5) Patients with a history (any grade) of immunotherapy induced colitis or pneumonitis based on clinical assessment and/or confirmed by biopsy.

(6) Patients with any of the following CNS metastases:

(a) Patients who have developed new or progressive brain metastasis within three months following prophylactic and/or therapeutic cranial radiation (whole brain or stereotactic radiation) as defined by imaging;

(b) Patients with symptomatic CNS metastases;

(c) Patients with carcinomatous meningitis.

(7) Unable to discontinue the use of strong CYP3A4 or UGT1A1 inhibitors at least 1 week or strong CYP3A4 inducers at least 2 weeks prior to receiving the first dose of irinotecan liposome injection. (See Section 5.4.2 for list of prohibited therapies).

(8) Have a previous or concurrent cancer that is distinct in primary (non-pulmonary) site or histology, except carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors (Ta and Tis [carcinoma in situ]) or any previous cancer curatively treated with last specific treatment >3 years ago without evidence of recurrence.

(9) Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives (whichever is less) of the investigational agent prior to the first scheduled day of dosing in this study.

Hematologic, Biochemical and Organ Function Exclusion Criteria

(10) Severe cardiovascular and pulmonary disease (e.g. myocardial infarction, unstable angina pectoris, coronary angioplasty or stenting, deep vein thrombosis, stroke, pulmonary fibrosis, active uncontrolled bleeding, or a known bleeding diathesis) less than 6 months before inclusion.

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

(12) Active infection (e.g. acute bacterial infection, tuberculosis, active hepatitis B or active human immunodeficiency virus) which in the Investigator's opinion might compromise the patient's participation in the trial or affect the study outcome.

(13) Known hypersensitivity to any of the components of irinotecan liposome injection, other liposomal products, or topotecan.

(14) Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhea > Grade 1.

Additional Disease Specific Exclusion Criterion (only applicable in France, per request of French Regulatory Authorities)

(15) Patients who, per investigator assessment, are suitable for a second line platinum-based regimen following relapse after first-line platinum-based therapy.

4.3 Patient Discontinuation

4.3.1 Permanent Discontinuation of Study Treatment

It is intended that patients will be treated until radiologically determined progressive disease per local radiology review and/or investigator assessment, per RECIST Version 1.1 criteria (or RANO-BM for CNS lesions in Part 2) or unacceptable toxicity. However, a patient may permanently discontinue study treatment at any point. Criteria for permanent discontinuation of study treatment for patients receiving irinotecan liposome injection (Part 1 and Part 2) and those receiving topotecan (Part 2) include:

- Radiologically determined progressive disease local radiology review and/or per investigator assessment, per RECIST Version 1.1 (or RANO-BM for CNS lesions in Part 2);
- Clinical deterioration sufficient to prevent further radiological assessment;
- Unacceptable toxicity, defined as a study drug related AE, prior to disease progression, which:
  - in the opinion of the Investigator, precludes ANY further treatment with study drug
  - requires treatment with study drug to be withheld for more than 14 days, unless in the opinion of the Investigator the patient is receiving benefit overall from the study treatment
  - would result in a third dose reduction in study drug (in a patient having already experienced 2 previous dose reductions) Detailed rule of dose modification can be found in Section 5.3.
- Development of an intercurrent medical condition or need for concomitant therapy that precludes ANY further treatment with study drug;
- Withdrawal of consent for further treatment;
- Pregnancy.

A patient who permanently discontinues study treatment and has **not** withdrawn from the study and must continue with all ongoing protocol requirements, as detailed in Section 4.3.3.

4.3.2 Withdrawal from the Study

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

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

4.3.3 Procedures following Study Drug Discontinuation or Study Withdrawal

Following permanent study drug discontinuation all procedures and evaluations required at the 30-day (End of Treatment) follow-up visit should be completed. All patients who permanently discontinue study medication as a result of an AE must be followed until resolution or stabilization of the AE. Patients who permanently discontinue study drug prior to radiologically determined disease progression should continue to be assessed radiologically and complete QoL assessments every 6 weeks, until radiologically determined progressive disease per RECIST Version 1.1 (or RANO-BM for CNS lesions) has been documented or until the start of new anti-neoplastic therapy. Overall survival follow-up contacts should continue every month from the 30-day follow-up visit until death or study closure, whichever comes first. If a patient does not return to the clinic for follow-up visits, attempts should be made to contact the patient via phone, email, or mail. At least 3 documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient is considered lost to follow-up, the date of death may be captured from public records. Since OS is the primary endpoint it is extremely important to capture the date of death.

If a patient discontinues from the study treatment, the patient will continue to be followed up for survival status (including where appropriate through publicly available records). Ongoing survival follow-up must be documented in both the source hospital records and the electronic case report form (eCRF).

If a patient withdraws consent to participate in the study at any point, a complete final evaluation at the time of the patient's withdrawal should be made with an explanation of the reason for withdrawal.

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

4.4 Enrollment of Additional Patients (Patient Replacement)

For Part 1, if a patient discontinues study treatment before completing two doses of study treatment, for reasons other than a DLT, then that patient may be replaced by a new patient at the same dose level. For Part 2, there is no patient replacement.

4.5 Method of Assigning Patients to Treatment Groups

Part 1:

Patients will initially be allocated to the irinotecan liposome injection 85 mg/m^2 dose cohorts (according to the 6+6 design followed by enrollment of an additional 12 patients as described in Section 3.1). According to the DLT rules detailed in Section 3.1, patients may subsequently be allocated in cohorts to an irinotecan liposome injection dose level of 70 mg/m^2, as determined by the SRC.

Part 2:

Part 2 will be initiated upon passing the stopping criteria and based on the decision of the Sponsor in consultation with the study steering committee.

After all screening assessments have been completed and the first patient reported outcome assessment has been completed, eligible patients will be randomized using a computerized IRT, in a 1:1 ratio, to one of the following treatment arms:

- Arm A (experimental arm): irinotecan liposome injection (70 mg/m^2 based on the findings of Part 1)
- Arm B (control arm): IV topotecan.

Randomization must occur within 7 days of planned dosing when all eligibility criteria are confirmed. The randomization will be stratified based on the following factors:

- Region (North America vs. Asia vs. Other)
- Platinum sensitivity (sensitive vs. resistant)
- Performance status (ECOG 0 vs. 1)
- Prior immunotherapy (yes vs. no).

Platinum resistant patients are defined as patients with disease that either progressed during first-line platinum containing therapy or within 90 days of its completion. Platinum sensitive patients are defined as patients with disease that progressed after 90 days of completion of first line platinum containing therapy.

5 INVESTIGATIONAL PRODUCTS

5.1 Description of Irinotecan Liposome Injection

Irinotecan liposome injection is a sterile, white to slightly yellow opaque isotonic liposomal dispersion. Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrosofate salt. It will be supplied as sterile, single-use vials containing 43 mg irinotecan free base at a concentration of 4.3 mg/mL.

5.1.1 Storage and Handling of Irinotecan Liposome Injection

Irinotecan liposome injection must be stored refrigerated at 2 to 8°C, with protection from light. Diluted solution must be protected from light prior to infusion. Irinotecan liposome injection must not be frozen. Responsible individuals should inspect vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe. They must contact the Sponsor or its designee if they notice a problem with the study drug.

Irinotecan liposome injection must be diluted prior to administration. Because of the potential for microbial contamination during dilution, the solution for infusion should be used immediately, but may be stored at room temperature (15° to 30°C) for up to 4 hours prior to the start of the infusion. If necessary, the solution for infusion may be refrigerated (2° to 8°C) for up to 24 hours prior to use. The diluted solution must not be frozen, and should be protected from light.

5.1.2 Packaging and Labelling of Irinotecan Liposome Injection

Irinotecan liposome injection will be packaged in a multi-vial cardboard container. The individual vials, as well as the outside of the cardboard container, will be labelled in accordance with local regulatory requirements.

5.1.3 Administration of Irinotecan Liposome Injection

Irinotecan liposome injection will be administered at a dose of 85 mg/m^2 (strength expressed based on irinotecan free base; approximately equivalent to 100 mg/m^2 of the hydrochloric trihydrate salt) IV over 90 minutes, every 2 weeks in a 6-week cycle. Should the 85 mg/m^2 dose

be deemed to have unacceptable toxicity, the 70 mg/m^2 will be utilized (strength expressed based on irinotecan free base; approximately equivalent to 80 mg/m^2 of the hydrochloric trihydrate salt) IV over 90 minutes, every 2 weeks in a 6-week cycle. Note that following assessment of the available safety and efficacy data from Part 1 the 70 mg/m^2 dose was chosen for Part 2 (see Section 1.3.3.2).

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

The actual dose of irinotecan liposome injection to be administered will be determined by calculating the patient's body surface area (BSA) prior to each IP administration. Use of BSA calculation formula according to institutional standards is allowed. The Du Bois formula, which has been shown to be effective for estimating body fat in both obese and non-obese patients, is widely used in clinical practice, and may be utilized in the study at investigator discretion, if different from institutional standard. BSA is represented in m2, W is weight in kg, and H is height in cm,

$$\mathbf{BSA = 0.007184 \times W^{0.425} \times H^{0.725}}$$

Du Bois D, Du Bois EF (Jun 1916). "A formula to estimate the approximate surface area if height and weight be known". Archives of Internal Medicine 17 (6): 863-71. PMID 2520314. Retrieved 2012-09-09.

A ±5% variance in the calculated total dose will be allowed for ease of dose administration.

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

Irinotecan liposome injection vials are single-use vials; therefore, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

Dose reduction and supportive care measures are described in Sections 5.3 and 5.4.1, respectively.

5.1.3.1 Irinotecan Liposome Injection Premedication

All patients must be pre-medicated prior to irinotecan liposome injection infusion with at least standard doses of dexamethasone or equivalent other steroids, and a 5-HT3 antagonist, and/or equivalent other anti-emetics according to standard institutional practices. Use of diphenhydramine hydrochloride and acetaminophen is allowed as per institutional guidelines and as clinically indicated. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles

5.1.3.2 Toxicity of Irinotecan Liposome Injection

The most clinically important adverse reactions of irinotecan liposome injection are summarized below. For more detailed description of the additional adverse reactions, the IB should be consulted.

Diarrhea

Irinotecan liposome injection can cause severe and life-threatening diarrhea, which must be treated at first signs of onset. Patients may experience late onset diarrhea (after 24 hours following chemotherapy) and early onset diarrhea (within 24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction). An individual patient may experience both early and late-onset diarrhea. Irinotecan liposome injection is prohibited to be administered to patients with bowel obstruction.

Early onset diarrhea (occurring during or shortly after infusion of irinotecan) is usually cholinergic in nature. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. Early onset diarrhea of any severity is treated with IV or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated).

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

Neutropenia

Irinotecan liposome injection can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In patients with metastatic pancreatic cancer in the NAPOLI-1 study receiving irinotecan liposome injection/5-FU/LV, the incidence of Grade 3 or 4 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to White patients [13 of 73 (18%)]. Neutropenic complications should be managed promptly with antibiotic support. Granulocyte-colony stimulating factor (G-CSF) may be used to manage neutropenia at the Investigator's discretion.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed with irinotecan, however, 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 AEs. There is insufficient evidence to know whether these known adverse reactions of irinotecan are also associated with irinotecan liposome injection. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions occur.

Interstitial Lung Disease

Irinotecan HCl can cause severe and fatal interstitial lung disease. This adverse reaction has not yet been described with irinotecan liposome injection. Irinotecan liposome injection should be withheld in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Irinotecan liposome injection should be discontinued in patients with confirmed diagnosis of interstitial lung disease.

Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with irinotecan liposome injection 70 mg/m^2 in humans, administered to pregnant rats and rabbits during organogenesis. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should use a highly effective contraception method during treatment with irinotecan liposome injection and for one month following the final dose. Highly effective contraceptive methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (e.g. oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (e.g. oral, implantable, injectable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male partner has had a vasectomy.

Total abstinence from intercourse with male partners (periodic abstinence is not acceptable).

Care of Intravenous Site

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

Patients at Particular Risk

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

The PKs of irinotecan liposome injection have not been studied in patients with hepatic impairment. In a population PK analysis, patients with screening bilirubin concentrations of 1-2 mg/dL (N=19) had average steady state concentrations for total SN-38 that were increased by 37% compared to patients with screening bilirubin concentrations of <1 mg/dL (N=329); however, there was no effect of elevated ALT/AST concentrations on total SN-38 concentrations. No data are available in patients with bilirubin >2 mg/dL.

Acute Infusion Associated Reactions

Acute infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications. Infusion reactions, consisting of rash, urticarial, periorbital edema, or pruritus, occurring on the day of irinotecan liposome injection administration were reported in 3% of patients receiving

irinotecan liposome injection monotherapy or irinotecan liposome injection/5-FU/LV combination in the NAPOLI-1 study.

Management of Infusion Reactions

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

- Allergic reaction (i.e., a disorder characterized by an adverse local or general response from exposure to an allergen):
  - Grade 1: Transient flushing or rash, drug fever <38 °C (<100.4 °F); intervention not indicated
  - Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤ 24 hours
  - Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
- Anaphylaxis (i.e., a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death):
  - Grade 1: Not applicable
  - Grade 2: Not applicable
  - Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
  - Grade 4: Life-threatening consequences; urgent intervention indicated.

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

Grade 1

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

Grade 2

- Stop infusion
- Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen
- Resume infusion at 50% of the prior rate once infusion reaction has resolved
- Monitor patient every 15 minutes for worsening of condition
- For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 500 or 650 mg orally.

- Future infusions may be administered at a reduced rate (e.g. over 120 minutes for irinotecan liposome injection), at the discretion of the Investigator.

Grade 3

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

Grade 4

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

For patients who experience a second Grade 1 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 500 or 650 mg orally or as per institutional guidelines.

UGT1A1*28 Monitoring

UGT1A1*28 genotype will be collected on all patients and assessed centrally. Results will be provided to the site and to the Sponsor. Sites will be asked to include the result from the UGT1A1*28 genotyping on the adverse events reporting form.

All patients treated with irinotecan liposome injection, regardless of the results of the UGT1A1*28 genotype, will be treated with the same starting dose of irinotecan liposome injection and will follow the same dose reduction rules. During the regular safety monitoring of patients during the study, as will be conducted by the Sponsor Medical Monitor(s) and by the SRC (Part 1) and the DMC (Part 2), the safety and PK of UGT1A1*28 homozygous patients will be compared to those who are non-homozygous for UGT1A1*28 to determine whether any different dosing strategy (such as a lower starting dose and/or different dose reduction for irinotecan liposome injection) is required for patients who are homozygous for UGT1A1*28. The first safety DMC meeting will occur after the 30th patient completed one cycle of treatment or discontinued treatment, whichever occurs first. No association between UGT1A1*28 and safety is expected in patients treated with topotecan.

Other Potential Toxicities

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

5.2 Description of Topotecan for Injection

The following information has been obtained from the HYCAMTIN® (topotecan) for injection US and EU package inserts. In the US, topotecan for injection, as a single agent, is indicated for the treatment of patients with SCLC with platinum-sensitive disease who progressed after first-line chemotherapy (Topotecan USPI). In the EU, IV topotecan is indicated for the

treatment of patients with relapsed SCLC for whom re-treatment with the first-line regimen is not considered appropriate (Topotecan SmPC).

5.2.1 Storage and Handling of Topotecan

5.2.1.1 US package insert/EU SmPC

Instructions for storage and handling of topotecan are provided in the pharmacy manual and the commercial package inserts and SmPCs.

5.2.2 Packaging and Labelling of Topotecan

Commercial topotecan sourced centrally by the Sponsor or sourced locally by the sites, where allowed by local regulations and approved by the Sponsor, will be labeled as investigational medicinal product in accordance with local country requirements.

5.2.3 Administration of Topotecan

Topotecan is administered at an initial dose of 1.5 mg/m^2 IV over 30 minutes daily for 5 consecutive days, every 3 weeks in a 6-week cycle.

Patients randomized to the topotecan arm should be considered for prophylactic G-CSF in all cycles starting 24 hours following the last dose (both short and long acting growth factor is acceptable, based on investigator preference).

5.3 Rules for Dose Modification of Irinotecan Liposome Injection and Topotecan

Dose modifications of irinotecan liposome injection and topotecan are allowed as clinically indicated (Section 5.3.1 and Section 5.3.2 respectively). If a patient's dose is reduced during the study, it should remain reduced for the duration of the study, dose re-escalation is not permitted.

5.3.1 Irinotecan Liposome Injection

Dose reduction and supportive care measures are described in Table 1, below.

Prior to initiating a new dose of treatment, a patient must have:

- Absolute neutrophil count (ANC) ≥ 1500/mm^3 (1.5x10^9/L)
- Platelet count ≥ 100,000/mm^3 (100x10^9/L)
- All local lab results assessed.

All clinical decisions will be based on local laboratory assessments. Treatment should be delayed for recovery from toxicity and upon recovery to at least Grade 1, treatment should be administered according to the guidelines in Table 1 below. If the patient had febrile neutropenia, the ANC must have resolved to ≥1500/mm^3 (1.5x10^9/L) and the patient must have recovered from infection.

Table 1: Recommended Dose[a] Modifications for Irinotecan Liposome Injection

Toxicity *NCI CTCAE Grade*[b]	**Occurrence**	**Starting Dose**	
		70 mg/m^2	**85 mg/m^2**
Hematological toxicities:			
Neutropenia, leukopenia, or thrombocytopenia *Grade 3 or 4* Neutropenic fever	**First occurrence**	56 mg/m^2 (80% of original dose)	68 mg/m^2 (80% of original dose)
	Second occurrence	46 mg/m^2 (65% of original dose)	55 mg/m^2 (65% of original dose)
	Third occurrence	35 mg/m^2 (50% of original dose)	43 mg.m^2 (50% of original dose)
• A new dose of treatment should not begin until the absolute neutrophil count is ≥1500/mm^3 (1.5x10^9/L) • A new dose of treatment should not begin until the platelet count is ≥100,000/mm^3 (100x10^9/L)			
Nonhematological toxicities:			
All nonhematological toxicities (except asthenia and anorexia): *Grade 3 or 4*	Withhold irinotecan liposome injection. Upon recovery to ≤ Grade 1, resume irinotecan liposome injection as below:		
	First occurrence	56 mg/m^2 (80% of original dose)	68 mg/m^2 (80% of original dose)
	Second occurrence	46 mg/m^2 (65% of original dose)	55 mg/m^2 (65% of original dose)
	Third occurrence	35 mg/m^2 (50% of original dose)	43 mg/m^2 (50% of original dose)
• A new dose of treatment should not begin until serum chemistry parameters resolve to ≤ Grade 1 • A new dose of treatment should not begin until nonhematological toxicities resolve to ≤ Grade 1 • For Grade ≥ 3 nausea and vomiting, reduce dose only if occur despite optimal anti-emetic therapy • Asthenia and Grade 3 anorexia do not require any dose modifications			
Interstitial lung disease	**First occurrence**	Discontinue treatment	
Severe hypersensitivity reaction	**First occurrence**	Discontinue treatment	

[a] All doses mentioned are based on irinotecan free base
[b] National Cancer Institute Common Terminology Criteria for Adverse Events Version 5

5.3.2 Topotecan for Injection

It is important to ensure that patients randomized to topotecan achieve the maximum possible exposure to ensure that they derive the most benefit from the treatment. Dose modifications (dose delays, including dose holidays, dose reductions), prophylactic use of myeloid growth factors, antibiotics for high risk patients and all other appropriate supportive care measures should be used to ensure that patients receive the highest tolerated dose and duration possible.

In exceptional circumstances (e.g. long holidays), where administration of the topotecan IV is not possible for 5 consecutive days, after discussion with study medical monitor, the Investigator can adjust the dosing regimen based on their clinical judgment to ensure:

(1) The patient is receiving highest tolerable dose and duration possible, and

(2) The highest daily dose does not exceed 1.5 mg/m^2.

The recommended dose modifications are described in this section (Section 5.3.2) for topotecan and the recommended supportive care measures are described in Section 5.4.1.

Topotecan should only be started in patients with a screening neutrophil count of greater than or equal to 1,500/mm^3 (1.5x10^9/L) and a platelet count greater than or equal to 100,000/mm^3 (100x10^9/L).

In subsequent cycles topotecan should not be administered unless the neutrophil count is ≥1x10^9/L, the platelet count is ≥100 x 10^9/L, and the hemoglobin level is ≥9 g/dL (after transfusion if necessary). Treatment should be administered according to the guidelines in Table 2 below.

Dose reduction of topotecan is allowed at investigator discretion during the treatment cycle as clinically indicated after the starting dose of 1.5 mg/m^2 is initiated.

Dose reduction from dose level 0 to dose level -2 is permitted. The reduced dose should continue to be administered over 5 consecutive days per topotecan prescribing information. Prophylactic antibiotics are recommended for patients at high risk of infectious complications.

Up to two dose reductions of topotecan per patient are permitted due to toxicities (see Table 2). If a third dose reduction is needed to manage a toxicity, topotecan treatment can be adjusted per clinical assessment after discussion with the Medical Monitor and documented appropriately.

Table 2: Recommended Topotecan Dose Modification Scheme for Subsequent Cycles

Dose Level	Dose Modifications
0	1.5 mg/m^2 IV days 1-5
-1	1.25 mg/m^2 IV days 1-5
-2	1.0 mg/m^2 IV days 1-5

The dose of topotecan in patients should be reduced to 0.75 mg/m^2/day for 5 consecutive days if the creatinine clearance is between 20 and 39 mL/min.

Topotecan should be discontinued if a new diagnosis of interstitial lung disease is confirmed.

Please note that for both irinotecan liposome injection and topotecan, all dose modifications should be based on worst preceding toxicity and a patient may permanently discontinue study treatment if he/she meets any of the criteria for permanent discontinuation of study treatment listed in Section 4.3.1.

5.4 Concomitant and Prohibited Therapies

5.4.1 Concomitant and Supportive Care Therapies

5.4.1.1 Antiemetic Medications

Irinotecan Liposome Injection: Dexamethasone and a 5-HT3 blocker (e.g., ondansetron or granisetron) will be administered as premedications to all patients receiving irinotecan liposome injection. Antiemetics may be prescribed as clinically indicated during the study period. An NK1 inhibitor, such as rolapitant (with no CYP3A4 interactions), for delayed nausea and vomiting for moderately emetogenic chemotherapy may be used in addition to 5-HT3 antagonist, as per institutional standards and as clinically indicated, with consideration of potential drug-drug interaction (please refer to list of prohibited medications in Section 5.4.2).

Topotecan: Antiemetic therapy for topotecan per institutional standard of care, including 5-HT3 antagonists and NK-1 inhibitor Rolapitant, may be prescribed as clinically indicated during the study period.

5.4.1.2 Myelosuppression

Use of G-CSF is permitted. All patients randomized to the topotecan arm are recommended to receive prophylactic G-CSF in all cycles starting 24 hours following the last dose (both short and long acting growth factor is acceptable, based on investigator preference). For patients receiving irinotecan liposome injection the use of prophylactic G-CSF (both short and long acting growth factor is acceptable, based on investigator preference) is allowed, based on investigator judgment. History of prior abdominal radiation increases the risk of severe neutropenia and febrile neutropenia following irinotecan liposome injection treatment. Close monitoring of blood counts is recommended, and the use of myeloid growth factors should be considered for patients with a history of radiation. Caution should be exercised in patients receiving concurrent administration of irinotecan liposome injection with irradiation. Prophylactic antibiotics are recommended for patients at high risk of infectious complications.

5.4.1.3 Therapy for Diarrhea

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

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

For a detailed algorithm of diarrhea management for chemotherapy-induced diarrhea see Appendix 1.

5.4.2 Prohibited Therapies

In the prescribing information for the treatment of patients with metastatic adenocarcinoma of the pancreas, after disease progression following gemcitabine-based therapy, the following drugs are noted as interacting with irinotecan liposome injection when administered in combination with 5-FU and LV (including but not limited to):

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

Treatment with these agents and any others that interact with irinotecan or topotecan should be avoided wherever possible. Refer to the IB for ONIVYDE® and topotecan instructions leaflet (as prepared and packaged for this study) for any other drug interactions.

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

- Other systematic anti-neoplastic therapy, (e.g. cytotoxics, targeted agents, immunotherapy, or antibodies, etc.).
- Radiotherapy, unless given for palliative reason and with the approval of the Medical Monitor. Study treatment must be held during palliative radiation and for 2 weeks after completion of radiation.
- Any other investigational therapy is not permitted.

5.5 Accountability of Study Drug

Investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of all study drugs used throughout the study, including locally sourced and centrally sourced supplies, as applicable. A record of all vials of study drug received and administered will be maintained on an investigational drug inventory form provided by the Sponsor. The following information will be recorded:

- Date and quantity of study drug received
- Date and quantity of study drug dispensed from the pharmacy per patient
- Date and quantity of study drug administered to each patient
- Date and quantity of study drug destroyed (if prepared and dispensed, but not administered for any reason, the study drug may not be returned to inventory)
- Date and quantity of study drug returned to sponsor.

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

During monitoring, the Sponsor's monitor will reconcile the information on the investigational drug inventory form with the actual amount of study drug remaining at each site. At the end study, all used and unused vials can be destroyed on site as per local regulations and instructions, or shipped to the Sponsor's storage facility for destruction. A certificate of destruction will be provided by the site or the storage facility for filling in the Investigator's file.

6 STUDY ASSESSMENTS

See Section 7.1 and Section 7.2 for schedule of assessments.

6.1 Screening Visit

The screening phase will begin once the patient signs the informed consent form. All procedures for screening are outlined in Section 8. For further descriptions of the clinical and laboratory assessments required, please refer to Section 9. Rescreening is only allowed after discussion and approval from the Sponsor's Medical Monitor.

6.2 Treatment/Active Follow-up Visits

Patients who are confirmed to meet all inclusion and exclusion criteria will be enrolled in Part 1 and randomized via an IRT in Part 2. The first dose (Cycle 1 Day 1) must be given within 7 days of enrollment/randomization. All study procedures and assessments are outlined in Section 8

and Section 9. During the treatment period, a window of ±2 days will apply to all visits, unless otherwise stated.

While in the Treatment/Active Follow-up phase, pauses in study drug treatment may be allowed, at the discretion of the Investigator. If a pause occurs in treatment, patients should continue to follow the same schedule of assessments, however, once 30 days have passed since last study drug administration, visits may be limited to every 3 weeks rather than weekly.

6.2.1 Pauses in Treatment

It is intended that all patients will be treated until progressive disease or unacceptable toxicity. Patients may take a treatment holiday and resume study treatment under one of the following instances:

- Patients with at least stable disease at the end of Cycle 3 may take a treatment holiday or may continue study treatment at the Investigator discretion as long as the Investigator believes that there is clinical benefit from continued study treatment.
- Patients who discontinue study treatment due to unacceptable toxicity prior to disease progression may resume study treatment if their underlying disease progresses and they recovered from the toxicity following discussion with the Investigator and in agreement with the Sponsor Medical Monitor.
- Patients who require palliative radiotherapy must withhold study treatment during palliative radiation and for 2 weeks after completion of radiation. These patients may resume study treatment following completion of radiotherapy, regardless of whether progression occurred or not, if continuation of study treatment is felt to be in the best interest of the patient in the judgment of the Investigator.
- In case of suspected or confirmed COVID-19 infection, administration of study treatment may be temporarily discontinued depending on the patient clinical presentation. In some cases, the Investigator may request a patient to be retested before administration of study treatment is resumed. (See also Section 10.1.2 for the reporting of COVID-19 infection).

In exceptional circumstances (e.g. long holidays), where administration of the topotecan IV is not possible for 5 consecutive days, after discussion with the study medical monitor, the Investigator can adjust the dosing regimen based on their clinical judgment to ensure:

(1) The patient is receiving highest tolerable dose and duration possible, and

(2) The highest daily dose does not exceed 1.5 mg/m^2.

Please note that the duration of a treatment holiday should NOT be longer than 1 cycle (6 weeks). More than one treatment holiday is allowed as long as the above criteria are satisfied.

During treatment breaks, QoL assessments and RECIST (or RANO-BM for CNS lesions in Part 2) scans should continue to follow the same frequency (every 6 weeks). All remaining assessments only need to be completed when/if the patient comes in to clinic for a scan or QoL assessment during this break, with the exception of safety monitoring, complete blood counts (CBCs) and serum chemistry collection. Safety monitoring and labs should be collected at a reduced rate of a minimum of every 3 weeks since last clinic visit, or at a higher frequency based on investigator judgment. If/when a patient restarts treatment, the cycle 2 and beyond schedule should be resumed.

6.3 30-day Follow-up Visit

All patients are expected to complete a 30-day follow-up assessment upon permanent discontinuation of study treatment. This assessment should occur approximately 30 days (± 1 week) after a decision is made to permanently discontinue study treatment (defined as patients with progressive disease **whilst receiving study treatment** and/or those assessed by

the Investigator as unable to continue or resume study treatment due to unacceptable toxicity) All procedures and assessments are outlined in Section 7.

6.4 Survival or Long-Term Follow-up

After the 30-day follow-up visit, patients should continue to be followed for survival status once every month (± 14 days) via clinic visit, telephone, email, or medical record review until death, lost to follow-up, withdrawal of consent (to further survival follow-up), or study closure, whichever occurs first. Additionally, data on subsequent anti-cancer treatments and the date of progression associated with subsequent anti-cancer treatment should be collected during these contacts and documented in the eCRF. In the case of patients who discontinue protocol treatment, for reasons other than progressive disease per RECIST Version 1.1 and/or RANO-BM criteria, and remain on study, disease evaluations (including imaging studies) and QoL assessments should continue into the follow-up period, as described in the Section 7.

If a patient does not respond to attempts to contact for OS follow-up, at least three documented attempts, including one via certified mail, should be made to contact the patient before declaring a patient lost to follow-up. If the patient does not respond to these requests, the date of death should be captured from public records if available.

7 SCHEDULE OF ASSESSMENTS

The schedule of assessments for irinotecan liposome injection is shown in Section 7.1 (Table 3) and IV topotecan in Section 7.2 (Table 4).

If the COVID-19 pandemic prevents patients from coming to the site, patients can have their study visit assessments performed remotely as judged appropriate by the Investigator. Please also refer to Appendix 15.4. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

7.1 Irinotecan Liposome Injection

The schedule of assessments shown in Table 3 below, only applies to patients receiving irinotecan liposome injection:

Table 3: Schedule of Assessments for Patients Receiving Irinotecan Liposome Injection

Procedure	Screening Visit	Treatment/Active Follow-up Visits											30 Day Follow-up[10]	LTFU (q1mo)[15]
		Cycle 1						Cycle 2 and beyond				Treatment Pause[16]		
		D1	D8	D15	D22	D29	D36	D1	D15	D22	D29			
Informed consent	X[1]													
Medical history	X[1]													
Demographics	X[1]													
Vital signs & weight	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam[3]	X[1]	X		X		X		X	X		X	X	X	
ECOG PS Scoring	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	
CBC with differential[4]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[4, 5]	X[2]	X	X	X		X		X	X		X	X	X	
Pregnancy test[6]	X[2]	X[2]						X					X	
UGT1A1*28 genotype	X[1]													
Tumor assessment[7]	X[1]	Every 6 weeks from C1D1										X	X	
QoL Questionnaires[8, 13]	X[17]	Every 6 weeks from C1D1										X	X	
ECG[8]	X[2]	X[12, 14]	X[12, 14]	X[12, 14]										
Archived tumor tissue		X												
Concomitant medications	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant procedures	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization (Part 2)	X[2]													
Biobanking[9]		X[8]	Collected at 6 and 12 weeks[8]											
PK samples[11]		X	X	X						X[11]				
Irinotecan liposome injection administration[18]		X		X		X		X	X		X			
Adverse event reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	
Overall survival reporting[15]														X

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C=cycle; CBC=cell blood count; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; LTFU=long-term follow-up; PK=pharmacokinetic; PS=performance status; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumors; RANO-BM=Response Assessment in Neuro-oncology brain metastases; RBC=red blood cell; RNA=ribonucleic acid; WBC=white blood cell

1 Within 28 days of C1D1.

2 Within 7 days of C1D1.

3 Physical Exams should occur on days of dosing prior to study drug administration. Height should be collected at screening only.

4 Day 1: within ≤3 days prior to infusion for all cycles, as applicable. Investigators must document their review of each laboratory report. The CBC will include the following: hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and other cells). Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium and phosphate.

5 A chemistry sample must be sent to the central lab; local lab results may be used for enrollment and dosing decisions if central lab results are not available.

6 Pregnancy tests should be performed via serum β-HCG within 7 days of C1D1 in the Screening period. During the Treatment period on D1 of every cycle and at the 30 day follow-up visit, a urine or serum β-HCG pregnancy test should be administered.

7CT and Brain MRI to be assessed at screening and every 6 weeks after the first dose of study drug regardless if the subsequent dose is delayed or interrupted. Please see Section 8.8 for further details.

In the event the patient permanently discontinues study treatment for reasons other than disease progression, a tumor assessment should be completed as soon as possible relative to the date of study termination, unless performed within the prior 4 weeks, to ensure disease progression is not present and to assess overall disease status. In such patients, tumor assessment should occur no later than the date of the 30-day follow-up visit and future assessments should continue to take place every 6 weeks during the follow-up period until objective disease progression or commencement of new anti-neoplastic therapy (in accordance with RECIST Version 1.1, (or RANO-BM for Part 2). Tumor assessment comprises imaging of both peripheral disease and the brain at each assessment.

8 To be assessed or collected prior to dosing.

9 Biobanking samples, whole blood for DNA, RNA, circulating free DNA and plasma and stool samples will only be collected for those individuals who have signed the optional biobanking informed consent for exploratory biomarkers at baseline (C1D1), as well as 6 and 12 weeks, (end of study. If a patient progresses prior to 12 weeks, a sample should be taken at time of discontinuation. “X" at D1 in Cycle 2 and beyond to include C3D1.

10 The 30-day follow-up visit should occur 30 days after discontinuation of the study treatment (± 1 week).

11 Please refer to Section 9.5 for details on PK sampling. An optional sample may also be provided during Days 2 to 6 (Part 2). Cycle 1 Day 8 sampling may occur ±1day.

12 Replicate ECG readings (Holter monitoring) will be collected on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15 at the same time point at PK assessments for patients in Part 1 only unless also required for Part 2 at the discretion of the Sponsor. Please refer to Section 8.7 for time points

13 Quality of life questionnaires (EQ5D and EORTC-QLQ-C30 +LC13, Patient Global Impression of Change, and Patient Global Impression of Severity) are collected in Part 1 and Part 2 and intended to be collected on day of dosing, prior to dosing every 6 weeks, and prior to any other assessment procedures. In the event the patient permanently discontinues study treatment for reasons other than disease progression, QoL assessments should continue to take place every 6 weeks during the follow-up period until objective disease progression or commencement of new anti-neoplastic therapy. A ±1-week window is permitted in order to sync assessment with clinic visit. The Patient Global Impression of Change is omitted at the screening assessment.

14 Part 1 only

15 Follow-up should occur every 1 month (± 2 weeks).

16 Treatment Pause Modified Schedule: During treatment breaks, QoL assessments and radiological assessments should continue to follow the same frequency (every 6 weeks). All remaining assessments only need to be completed when/if the patient comes in to clinic for a scan or QoL assessment during this break with the exception of safety monitoring, CBCs and serum chemistry collection. Safety monitoring and labs should be collected at a reduced rate of a minimum of every 3 weeks since last clinic visit, or at a higher frequency based on investigator judgment. If/when a patient restarts treatment, the cycle 2 and beyond schedule should be resumed.

17 Within 14 days of C1D1.

18 Between 48 and 72 hours after completion of the irinotecan liposome injection infusion, a safety follow-up phone call will be made by a study nurse.

7.2 IV Topotecan

The schedule of assessments shown in Table 4, below, only applies to patients receiving IV topotecan:

Table 4: Schedule of Assessments for Patients Receiving IV Topotecan

Procedure	Screening Visit	Treatment/Active Follow-up Visits											30 Day Follow-up[10]	LTFU (q1mo)[12]
		Cycle 1						Cycle 2 and beyond				Treatment Pause[13]		
		D1	D8	D15	D22	D29	D36	D1	D15	D22	D29			
Informed consent	X[1]													
Medical history	X[1]													
Demographics	X[1]													
Vital signs & weight	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam[3]	X[1]	X			X			X		X		X	X	
ECOG PS Scoring	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	
CBC with differential [4]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[4, 5]	X[2]	X	X		X			X		X		X	X	
Pregnancy test[6]	X[2]	X[2]						X					X	
UGT1A1*28 genotype	X[1]													
Tumor assessment[7]	X[1]	Every 6 weeks from C1D1										X	X	
QoL Questionnaires[8, 11]	X[14]	Every 6 weeks from C1D1										X	X	
ECG[8]	X[2]													
Archived tumor tissue		X												
Concomitant medications	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant procedures	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization	X[2]													
Biobanking[9]		X[8]	Collected at 6 and 12 weeks[8]											
Topotecan Administration (5 consecutive days)		X			X			X		X				
Adverse event reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	
Overall survival reporting[12]														X

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C=cycle; CBC=cell blood count; D=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; PK=pharmacokinetic; PS=performance status; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumors; RANO-BM=Response Assessment in Neuro-oncology brain metastases; RBC=red blood cell; RNA=ribonucleic acid; WBC=white blood cell

1 Within 28 days of C1D1.
2 Within 7 days of C1D1.
3 Physical Exams should occur on days of dosing prior to study drug administration. Height should be collected at screening only.
4 Day 1: within ≤ 3 days prior to infusion for all cycles, as applicable. Investigators must document their review of each laboratory report. The CBC will include the following: hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and other cells). Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), BUN, serum creatinine, glucose, bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium and phosphate.
5 A chemistry sample must be sent to the central lab; local lab results may be used for enrollment and dosing decisions if central lab results are not available.
6 Pregnancy tests should be performed via serum β-HCG within 7 days of C1D1 in the Screening period. During the Treatment period on D1 of every cycle and at the 30 day follow-up visit, a urine or serum β-HCG pregnancy test should be administered.
7 CT and Brain MRI to be assessed at screening and every 6 weeks first dose of study drug even if subsequent dose is delayed or interrupted. Please see Section 8.8 for further details.
In the event the patient permanently discontinues study treatment for reasons other than disease progression, a tumor assessment should be completed as soon as possible relative to the date of study termination, unless performed within the prior 4 weeks, to ensure disease progression is not present and to assess overall disease status. In such patients, tumor assessment should occur no later than the date of the 30-day follow-up visit and future assessments should continue to take place every 6 weeks during the follow-up period until objective disease progression or commencement of new anti-neoplastic therapy (in accordance with RECIST Version 1.1 (or RANO-BM) for Part 2). Tumor assessment comprises imaging of both peripheral disease and the brain at each assessment.
8 To be assessed or collected prior to dosing.
9 Biobanking samples, whole blood for DNA, RNA, circulation free DNA, plasma, and stool samples will only be collected for those individuals who have signed the optional biobanking informed consent for exploratory biomarkers at baseline (C1D1), as well as 6 and 12 weeks, (end of study). If a patient progress prior to 12 weeks, a sample should be taken at time of discontinuation. "X" at D1 in Cycle 2 and beyond to include C3D1.
10 The 30-day follow-up visit should occur 30 days after discontinuation of the study treatment (± 1 week).
11 Quality of life questionnaires (EQ5D and EORTC-QLQ-C30 +LC13, Patient Global Impression of Change, and Patient Global Impression of Severity) are collected in Part 1 and Part 2 and are intended to be collected on day of dosing, prior to dosing every 6 weeks, and prior to any other assessment procedures. In the event the patient permanently discontinues study treatment for reasons other than disease progression, QoL assessments should continue to take place every 6 weeks during the follow-up period until objective disease progression or commencement of new anti-neoplastic therapy. A ± 1-week window is permitted in order to sync assessment with clinic visit. The Patient Global Impression of Change is omitted at the screening assessment.
12 Follow-up should occur every 1 month (± 2 weeks).
13 Treatment Pause Modified Schedule: During treatment breaks, QoL assessments and radiological assessments should continue to follow the same frequency (every 6 weeks). All remaining assessments only need to be completed when/if the patient comes in to clinic for a scan or QoL assessment during this break with the exception of safety monitoring, CBCs and serum chemistry collection. Safety monitoring and labs should be collected at a reduced rate of a minimum of every 3 weeks since last clinic visit, or at a higher frequency based on investigator judgment. If/when a patient restarts treatment, the cycle 2 and beyond schedule should be resumed.
14 Within 14 days of C1D1.

8 CLINICAL PROCEDURES AND ASSESSMENTS

8.1 Medical History

A medical history will include all pertinent prior medical conditions, treatments for small cell lung cancer, surgeries or other medical procedures. Medical history should also include a history of tobacco use.

8.2 Adverse Event Assessment and Reporting

Investigators should complete all routine and standard of care assessments to evaluate for AEs. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings. Adverse events should be reported throughout the course of the study, including during the 30 day follow-up period (or until death or withdrawal of consent if they occur before the end of this period).

8.3 Physical Exam

Physical examination will include a careful assessment of all body systems, including the skin; central and peripheral nervous system; eyes; ears, nose and throat; respiratory, musculoskeletal and cardiovascular systems; abdomen and extremities. Particular attention should be paid to areas of possible neoplastic involvement.

8.4 Vital Signs

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

8.5 Performance Status Assessment

The Eastern Cooperative Oncology Group (ECOG) performance status will be obtained by the Investigator or his/her designee by questioning the patient about their functional capabilities. A description of the ECOG performance status criteria is summarized in Appendix II.

8.6 Quality of Life Assessments

A quality of life assessment will be performed using the EQ-5D-5L and the EORTC-QLQ-C30 + LC13), to be collected via an electronic ePRO device. The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. Patient reported symptoms from EORTRC-QLQ are recorded on a 4-point scale with values ranging from 1 (no symptoms experienced at all) to 4 (symptomology experienced is very much). The EORTC QLQ-LC13 is a lung cancer specific module to be used in conjunction with the EORTC QLQ-C30. The LC13 covers typical symptoms of patients with lung cancer, such as cough, pain, dyspnea, sore mouth, peripheral neuropathy, hair loss (Koller, 2015) with 13 questions. The EORTC-QLQ-C30 + LC13 has a total of 43 questions. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

Two additional single item patient-reported outcomes assessments, the PGI-S and the PGI-C, will be administered at each quality of life assessment. The PGI-C is not included in the screening assessment, since the baseline assessment is not applicable for this instrument.

Patients in Parts 1 and 2 will be required to complete the QoL questionnaires at time points outlined in the Schedule of Assessments (at screening and every 6 weeks thereafter). On days that the patient is to receive study drug, assessments should be completed prior to study drug administration, and prior to any other assessment procedures. The first collection of quality of life assessments must be completed at screening. It is intended that questionnaires be completed

in clinic on days of dosing. A ± one-week window is allowed in order to assist synchronizing survey assessment with dosing. The sequence in which these questionnaires are completed should be as follows: the EORTC QLQ-C30 should be administered first, followed by the EORTC QLQ-LC13, the PGI-C and PGI-S, and the EQ-5D-5L in this order. The QoL questionnaires should be completed in a language that is understood by the patient. Only validated and approved translations can be used.

8.7 Electrocardiogram and Pharmacokinetic-Matched Holter Monitoring

At screening, for Part 1 and 2, a single 12-lead ECG will be performed to include a description of the cardiac rate, rhythm, interval durations, and an overall impression, to determine eligibility. This will be assessed locally by the Investigator.

Patients enrolled to Part 1 will undergo serial Holter monitoring ECG recordings and time-matched PK sampling. Holter monitoring comprises continuous ECG recording, and ECG extractions will be made via the vendor at the time points indicated within Table 7. ECG recordings will be time-matched with PK samples in order to assess any relationship between blood levels of irinotecan liposome injection and its metabolite SN-38 and possible QTcF interval changes, as shown in Table 5. Holter monitoring equipment will be provided, additional details regarding ECG collection should be followed in accordance with the central ECG manual.

Based on the results of the Part 1 Holter data analysis, additional Holter data may be collected in Part 2 at the discretion of the Sponsor.

Table 5: Part 1 PK and ECG Extraction Time Points

Part 1 PK and ECG Extraction Time Points				
Cycle, Day	**Time point**	**PK**	**ECG** (Holter monitoring, continuous ECG recording)	**ECG Recording Duration**
C1D1	Pre-dose	x	x	30 hours continuous
C1D1	End of irinotecan liposome injection infusion	x	x	
C1D1	2 hours after end of infusion (±1 hour)	x	x	
C1D2	Approximately 24 hours after end of irinotecan liposome injection infusion	x	x	
C1D8	Day of visit	x	x	5 hours
C1D15	Pre-dose	x	x	5 hours

PK samples are collected in Part 1 and Part 2, however the PK matched ECG extractions are only performed during Part 1.
C=cycle; D=day; ECG=electrocardiogram; PK=pharmacokinetic

8.8 Disease Evaluation

Tumor assessments will be performed at screening and every 6 weeks (± 1 week) from C1D1 using the RECIST guidelines Version 1.1 (Parts 1 and 2) and the RANO-BM criteria for CNS lesions (Part 2). All patients will have imaging of the brain at screening and at each restaging.

The tumor assessment at screening are:

- CT with contrast (chest/abdomen required and pelvis if clinically indicated)
- Brain MRI with contrast.

Baseline tumor assessments performed per standard of care within 28 days of enrollment are acceptable as long they are consistent with protocol requirements, and imaging data is available to transmit for central review per IMI ICON specifications.

The tumor assessment every 6 weeks (± 1 week) from C1D1 are:

- CT with contrast (chest/abdomen required and pelvis if clinically indicated)
- Brain MRI with contrast.

For patients who are allergic to IV contract or cannot tolerate IV contrast due to impaired renal function or other issues, a regular CT or MRI is acceptable. Each follow-up tumor assessment should use the same assessment method as performed at screening, unless medically contraindicated. Patients who discontinue study treatment for reasons other than disease progression by RECIST (or RANO-BM for CNS lesions in Part 2) should continue to be followed on the same schedule until radiological documentation of progressive disease (based on local radiology review and/or investigator's assessment) or start of another treatment. The Sponsor will collect and store all tumor measurement images on all patients throughout the study; however, progressive disease will be determined by local radiology review and/or investigator assessment. A review of the scans will be performed by the Sponsor for an independent analysis of PFS and ORR. Details of BICR tumor assessment process and approach will be described in a separate imaging charter document.

For Part 2 only, comparison of the rate of development/time to development of CNS progression and development of new CNS metastases (exploratory endpoint), tumor responses in the CNS will assessed using the response criteria developed by the Response Assessment in Neuro-oncology Brain Metastases (RANO-BM) working group (Lin 2015). See Appendix III for details of the RANO-BM response assessment.

9 LABORATORY PROCEDURES AND ASSESSMENTS

9.1 Complete Blood Count

The CBC will include the following: hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and other cells).

Local laboratory results may be used for enrollment and dosing decisions.

9.2 Serum Chemistry

Serum chemistry will include electrolytes (sodium, potassium, chloride and bicarbonate), blood urea nitrogen (BUN), serum creatinine, glucose, bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, uric acid, total protein, albumin, calcium, magnesium and phosphate.

A chemistry sample must be sent to the central laboratory; local laboratory results may be used for enrollment and dosing decisions.

9.3 Pregnancy Test

For women of childbearing potential, (refer to Section 4.2 Exclusion Criterion (2) for definition), pregnancy tests should be performed via serum β-HCG within 7 days of C1D1 in the Screening period. During the treatment period on D1 of every cycle and at the 30 day follow-up visit, a urine or serum β-HCG pregnancy test should be administered. At C1D1, the pregnancy test does not need to be repeated if already performed within 7 days of C1D1. Any positive urine pregnancy test must be confirmed via serum β-HCG.

9.4 UGT1A1*28

A whole blood sample will be collected and assessed centrally within 28 days of C1D1 to test for UGT1A1*28 genotype from all patients. The result is not needed prior to the initial dose of irinotecan liposome injection or topotecan, but the result will be provided to the site. All patients

receiving irinotecan liposome injection will receive the same starting dose regardless of their UGT1A1*28 genotype.

9.5 Pharmacokinetic Sampling

Plasma samples will be collected to determine the levels of irinotecan and SN-38. The PK time points are outlined in Table 6. PK samples will be collected during Parts 1 and 2 of the study.

Table 6: Pharmacokinetic Sampling Plan

Sample	Timepoint	Window
	Part 1:	
1	Cycle 1 Day 1 (Pre-Dose): prior to irinotecan liposomal injection	-24 hr
2	Cycle 1 Day 1 (Post-Dose): at the end of the irinotecan liposomal injection infusion.	+15 min
3	Cycle 1 Day 1 (Post-Dose): at 2 hours after end of the irinotecan liposomal injection infusion.	±1 hr
4	Cycle 1 Day 1 (Post-Dose): at 24 hours after end of the irinotecan liposomal injection infusion.	±6 hr
5	Cycle 1 Day 8: at any time of day.	±1 day
6	Cycle 1 Day 15 (Pre-Dose): prior to irinotecan liposomal injection infusion.	-24 hr
7	Cycle 2 Day 22: at any time of day.	±1 day
8	Early withdrawal visit: at any time of day.	
	Part 2	
1	**Cycle 1 Day 1 (Pre-Dose): prior to irinotecan liposomal injection**	**-24 hr**
2	**Cycle 1 Day 1 (Post-Dose): at the end of the irinotecan liposomal injection infusion.**	**+15 min**
3	**Cycle 1 Day 1 (Post-Dose): at 2 hours after end of the irinotecan liposomal injection infusion.**	**±1 hr**
4	**Cycle 1 Days 2 to 6 (optional sample*): anytime between 1 and 5 days after the start of irinotecan liposomal injection infusion.**	**±3 days**
5	**Cycle 1 Day 8: at any time of day.**	**±1 day**
6	**Cycle 1 Day 15 (Pre-Dose): prior to irinotecan liposomal injection infusion.**	**-24 hr**

For Part 2 of the study, PK samples are only expected for patients enrolled to the irinotecan liposome injection arm.

hr=hour; min=minutes

*Optional sampling: to be taken if the patient visits or is at the clinic on these days

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

Residual plasma samples used for irinotecan liposome injection and SN-38 analysis may also be used for exploratory analysis. This could include using leftover plasma samples for protein binding analysis, metabolite profiling or analysis of excipients. Plasma samples remaining from the analysis may be retained by the Sponsor for additional investigations (i.e. long-term stability, reproducibility and bioanalytical method cross-validation).

9.6 Biobanking

Biobanking is optional and will only be collected for those patients who have agreed to it by signing the specific informed consent form for the exploratory part of the study. Archival tumor tissue samples will be collected at baseline (C1D1), if available. Blood and stool samples at proposed timepoints will be collected as indicated in schedule of assessments Section 7:

- Plasma (5 mL, dry tube)
- Blood for RNA (2.5 mL, Paxgene RNA tube)

- Blood for DNA (2.5 mL, Paxgene DNA tube)
- Blood for cfDNA (10 mL, Streck tube)
- Stool sample (outlined in laboratory manual).

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

Samples will be archived in a central biorepository designated by the Sponsor and according to local administration regulations and/or the EMA and will not carry personal identification (such as patient's social security number or name). The samples will be destroyed no more than 15 years after the end of the main study or at the patient's request.

Blood samples are biobanked for future analysis of additional circulating markers, including proteins, pharmacogenetic and pharmacogenomic biomarkers (including potential genetic research).

Analysis from the biobank samples will be performed outside the scope of the main study and reported separately. Exploratory analysis techniques, including graphical representations, may be employed, including graphical representations, appropriate to examine relationships between the study endpoints and observed genotypes.

Only those designated by the Sponsor will be allowed access to the samples. All information collected will be kept strictly confidential and all clinical information will be anonymous. This means that no personally identifiable information will be retained with the results of the exploratory analyses, so that no individual or collective results will be linked to the individual patient whose sample was taken in the study. No individual genetic results will be communicated to the Investigator or patient unless required by local regulation. The Sponsor will comply with all local regulations related to the establishment, management and application of a human blood samples biobank.

10 ADVERSE EVENT REPORTING

10.1 Definitions

10.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily need to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, including abnormal laboratory findings, symptoms, or diseases temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Worsening of a medical condition of the underlying disease (e.g. progression of small cell lung cancer), for which the efficacy of the study drug is being evaluated will not be considered an AE in this study.

10.1.2 Serious Adverse Events

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

- Results in death.
- Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization (Exception: hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE. NOTE: Complications that occur

during hospitalization are AEs and if a complication prolongs hospitalization, then the event is serious).

- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly or birth defect.
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

In addition to the above criteria, the following is considered a medically important event and must be reported to the Sponsor under the SAE reporting rules in Section 10.3 within 24 hours of site awareness, irrespective of causality:

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

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

Any additional AE that the Sponsor or Investigator considers serious should be immediately reported to the Sponsor and included in the corporate SAEs database system. This includes any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation)).

10.2 Assessing and Documenting Adverse Events

Adverse event reporting will begin in conjunction with the signing of informed consent for the study. Investigators should complete all routine and standard of care assessments to evaluate for toxicity and symptoms of drug-induced AEs. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings.

All AEs, whether serious or not, will be described in the source documents and the AE page of the case report form. All new events, as well as those that worsen in intensity or frequency relative to screening, which occur after signing of informed consent and during the 30 day follow-up period, must be recorded. However, new AEs felt by the Investigator to be related to study treatment, must be reported any time the Investigator becomes aware of such an event, even if this occurrence is after the 30 day follow-up period. All AEs should be followed until resolution, until death or withdrawal of consent.

Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if they are medically relevant, e.g. symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

Information to be reported in the description of each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event
- The date of resolution of the event
- A determination of whether the event is serious or not
- A determination of relatedness to the study drug

- Action taken: none; change in the study drug administration (e.g., temporary interruption in dosing); drug treatment required; non-drug treatment required; diagnostic or concomitant procedure performed; patient discontinued from the study treatment (complete Treatment Termination case report form)
- Outcome: resolved without sequelae; resolved with sequelae; event ongoing; subject died (notify the Sponsor immediately, and complete the SAE page and the Subject Death page).

10.3 Reporting Serious Adverse Events

Serious adverse event reporting will begin in conjunction with the date of informed consent.

All fatal or life-threatening AEs must be immediately reported to the Sponsor or Contract Research Organizations (CRO's) medical team by telephone or e-mail. Within 24 hours of the event, the SAE form must be emailed to PPD whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

In case of accidental or intentional overdose of study drug (irinotecan liposome injection or topotecan), even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor immediately (within 24 hours) using the AE and SAE forms.

All other SAEs and any medically important events (Section 10.1.2) must be reported to the Sponsor within 24 hours by phone or e-mail. Details are outlined in the study procedure manuals. The SAE form must also be emailed to PPD within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known.

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

All SAEs will be evaluated by the Medical Monitor. If meeting the requirements for expedited reporting, the Sponsor will report the SAE to all regulatory authorities with jurisdiction over ongoing trials with the study drug, to the EC and to all other investigators involved in clinical trials with the study drug. The Investigator is responsible for reporting all SAEs to the appropriate IRB/EC, if appropriate according to local requirements.

10.4 Determining the Severity and Relatedness of an Event

10.4.1 Grading the Severity of an Adverse Event

Each AE will be graded according to the NCI CTCAE Version 5.0, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be designated as mild, moderate, severe, or life-threatening, or fatal which correspond to Grades 1, 2, 3, 4, and 5, respectively on the NCI CTCAE, with the following definitions:

Mild: an event not resulting in disability or incapacity and which resolves without intervention;

Moderate: an event not resulting in disability or incapacity but which requires intervention;

Severe: an event resulting in temporary disability or incapacity and which requires intervention;

Life-threatening: an event in which the patient was at risk of death at the time of the event;

Fatal: an event that results in the death of the patient.

10.4.2 Relationship to Study Drug

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

10.4.3 Reporting and Follow-up of Pregnancy

The Investigator must instruct all female patients to inform them immediately should they become pregnant during the study. The Investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. If the Investigator becomes aware of a pregnancy occurring in the partner of a male patient participating in the study, this should be reported to the Sponsor. Monitoring of the partner pregnancy should continue until conclusion of the pregnancy.

11 STATISTICAL METHODS

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

11.1 General Considerations

Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum).

The efficacy and safety of irinotecan liposome injection in Part 1 will be reported descriptively.

11.2 Statistical Hypothesis and Determination of Sample Size

Part 2

The primary endpoint is OS. The primary hypothesis will test whether OS is increased in patients treated with irinotecan liposome injection.

A total of 450 patients will be randomized in a 1:1 ratio to the two treatment arms. The primary OS test will be performed when at least 350 OS events are observed across the two treatment arms to provide at least 87% power to detect a true hazard ratio of HR ≤0.714 (median OS: 7.5 versus 10.5 months) using a stratified logrank test (stratified by region and platinum sensitivity) with overall 1-sided significance level of 0.025 (adjusted for interim analyses).

Assuming enrollment over 24 months with a ramp-up to a maximum of 21 patients per month and lost-to-follow-up rate of 5% across both treatment arms, the timing of the primary analysis is expected to be at 37 months.

An interim OS analysis for futility will be conducted when approximately 29% of the planned final number of OS events (i.e., approximately 100 of 350 OS events) has been observed in the ITT population. To control type I and type II errors, the planned interim analyses for OS will utilize an alpha and (non-binding) beta spending function approach with Hwang-Shih-Decani spending and γ parameter equal to -4.5 and -1 for each error type, respectively (Hwang, 1990). Non-binding for the futility indicates that the boundary will be constructed in such a way that it can be overruled if desired without inflating the type I or II error. Nominal alpha of 0.0001 will be spent at the supplemental interim analysis requested by FDA. Since the boundary is

dependent on the number of OS events, the actual boundary used will be re-calculated, incorporating the spending function as defined, based on the number of actual OS events analyzed at the time of the analyses and to reflect the nominal α spent at the supplemental interim analysis. P-boundary will be used as the criteria for the formal statistical inference.

The interim analysis specifications per the plan are provided in Table 7.

Table 7: Type I (α) and Type II (β) Error Spending for the Planned OS Analyses

		Futility				Efficacy			
Analysis	**D**	**$Z_{boundary}$**	**$p_{boundary}$**	**Cum β spend**	**HR_{crit}**	**$Z_{boundary}$**	**$p_{boundary}$**	**Cum α spend**	**HR_{crit}**
Interim	100	0.276	0.609	0.025	1.057	-3.181	0.001	0.001	0.529
Final	350	-1.967	0.025	0.13	0.810	-1.967	0.025	0.025	0.810

D = # of OS events at analysis. $Z_{boundary}$ is the critical test statistic value at which futility (< Z) or efficacy (> Z) would be concluded. $p_{bounday}$ is the critical one-sided p-value threshold for the comparison (>p for futility, <p for efficacy). HR_{crit} is the observed hazard ratio threshold (> HR for futility, < HR for efficacy).

The DMC will be responsible for evaluating the futility OS analysis and making a recommendation about early termination due to observed study results. At the time of the interim analysis, ORR by BICR tumor assessments will be analyzed descriptively by the independent DMC for the first 200 patients randomized in Part 2 of the study (i.e. approximately 100 patients from each arm). The independent DMC will notify the Sponsor if pre-specified criteria for ORR are met. A supplemental interim analysis is planned on data collected 24 weeks after the last patient has been randomized based on the ITT population to fulfill FDA recommendation. At this timepoint, OS and ORR (supported by duration of response (DOR)) will be summarized descriptively. Further detail on statistical analysis is provided in SAP. A Data Integrity Management Plan will also be created and finalized prior to the descriptive analysis of ORR at the time of the interim analysis to clearly describe the data handling approach and the data transfer and review pathway.

Key secondary endpoints are PFS, ORR, and change from baseline in patient-reported symptoms (dyspnea and cough).

Key secondary endpoints will be tested no more than once. To control the overall Type I error rate for the comparison between irinotecan liposome injection and topotecan for the primary and secondary endpoints, a hierarchical approach will be applied to the statistical testing of the secondary endpoints. The statistical inference for the first secondary endpoint of PFS (by BICR) will only be performed if the primary endpoint, OS, is statistically significant. The second secondary endpoint of ORR (by BICR) will only be tested if PFS is statistically significant. Similarly, the PRO endpoints will only be tested if ORR is statistically significant. Any parameter which is not statistically significant will be regarded as descriptive and exploratory. Further information on alpha control methods will be provided in the SAP.

Where treatment comparisons are by stratified analysis, stratification factors will be region and platinum sensitivity with classification according to the randomization designation.

Any additional data collected after primary and secondary analyses have been completed may be used in post-hoc analysis as deemed appropriate.

11.3 Analysis Populations

Patients enrolled and treated with at least one dose of irinotecan liposome injection will comprise the Part 1 safety and efficacy populations. The safety and efficacy of these patients will be presented descriptively.

Patients randomized in Part 2 will comprise the ITT population. This will be the population that is evaluated in comparison to evaluate the efficacy (OS, PFS, ORR) of the experimental arm.

In the ITT analyses of efficacy, each patient will be considered according to the randomized treatment assignment. Patients who received any dose of any study drug will define the Part 2 safety population.

Patient reported outcome (PRO) endpoints will be evaluated on the ITT.

The PK population will include all irinotecan liposome injection treated patients which received at least one dose, and who had at least one plasma concentration and no major protocol deviations affecting PK variables.

11.4 Disposition, Demographics, and Baseline Characteristics

Disposition of patients will be summarized, including those screened, randomized, treated, discontinued from treatment, and discontinued from study. Reasons for discontinuation will be tabulated. Demographic and baseline characteristics will be summarized. Medical history and prior medications will be tabulated.

11.5 Efficacy Analysis

11.5.1 Primary Efficacy Analysis (Part 2)

Overall survival is defined as the number of months from randomization in Part 2 to the date of death. Patients without observed death at the time of the primary analysis will have OS censored according to the last recorded date alive.

The primary analysis will be performed using a stratified log-rank test (stratified by region and platinum sensitivity) comparing the OS difference between two treatment arms with level of significance controlled at the one-sided 0.025 level. Kaplan-Meier methods will be used to estimate median OS (with 95% CI) and to display OS time graphically. A stratified Cox proportional hazards model will be used to estimate hazard ratio and its corresponding 95% CI. Sensitivity analyses for OS will be described in the SAP and will include subgroup analyses (according to levels of each stratification factor and other potential prognostic variables).

11.5.2 Key Secondary Analyses (Part 2)

Key secondary endpoints are PFS, ORR, and change from baseline in patient-reported symptoms (dyspnea and cough). Key secondary endpoints will be tested no more than once.

11.5.2.1 Progression-free Survival

Progression-free survival is the time from randomization in Part 2 to the first documented objective disease progression (PD) using RECIST Version 1.1 (or RANO-BM criteria for CNS lesions) or death due to any cause, whichever occurs first. Determination of PFS will be based on BICR tumor assessment, with PFS based on investigator tumor assessments as a sensitivity analysis. If neither death nor progression is observed, data will be censored on the date of the last observed tumor assessment date. Patients without a valid tumor response evaluation at enrollment/randomization will be censored on the date of enrollment/randomization. Patients starting a new anti-cancer treatment prior to documented PD will be censored at the date of the last observed tumor assessment prior to start of the new treatment. Patients with documented PD or death after an unacceptable long interval (i.e., 2 or more missed or indeterminate scheduled assessments) will be censored at the time of the last observed non-PD tumor assessment date prior to progression or death. Details of data handling for censoring of PFS will be provided in the SAP.

The difference in PFS between treatments will be evaluated using a stratified log-rank test (stratified by region and platinum sensitivity). Kaplan-Meier methods will be used to estimate median PFS (with 95% CI) and to display PFS time graphically. A stratified Cox proportional hazards model will be used to estimate the PFS hazard ratio and its corresponding 95% CI. Sensitivity analyses for PFS will be described in the SAP.

11.5.2.2 Objective Response

Objective response rate is the proportion of patients who achieve partial response (PR) or complete response (CR) according to RECIST Version 1.1 guidelines (or RANO-BM criteria for CNS lesions in Part 2). An estimate of the ORR and its 95% CI will be calculated. The difference in ORR between treatment groups will be compared using Cochran-Mantel-Haenszel method, incorporating analysis stratification factors (region and platinum sensitivity).

In addition to investigator assessment, a BICR review of the tumor assessment images will be performed for all patients included in the study, and more specifically at the time of:

- the interim analysis for the descriptive analysis of ORR based on the first 200 patients randomized in both arms (i.e. approximately 100 patients from each arm), as well as for the patients included in Part 1 and treated with the selected dose for Part 2.
- the supplemental interim analysis, for tumor images for all randomized patients collected 24 weeks after last patient has been randomized

A final formal test on secondary endpoint ORR will be based on BICR tumor assessment, with ORR based on investigator tumor assessments as a sensitivity analysis.

11.5.2.3 Change From Baseline in Dyspnea and Cough Symptoms

The efficacy of irinotecan liposome injection compared to topotecan on dyspnea and will be evaluated considering the response to treatment in terms of:

- Change from baseline to Week 12 in patient's perceived dyspnea, as measured by EORTC QLQ-C30/LC13
- Change from baseline to Week 12 in patient's perceived cough, as measured by EORTC QLQ-LC13

Change from baseline defined as post-baseline value minus baseline value will be calculated for each assessment.

Change from baseline at Week 12 in dyspnea/cough will be analysed using an ANCOVA model with covariates treatment group, stratification factors (region, platinum sensitivity, performance status, prior immunotherapy), and PRO score at baseline. Patients having missing baseline, Week 6, or Week 12 dyspnea/cough score will have their missing dyspnea score imputed under the Missing at Random (MAR) assumption using the multiple imputation (MI) methodology in the primary analysis, and under the missing not at random (MNAR) assumption in the sensitivity analysis. Detailed analysis methods for PRO endpoints will be discussed in the SAP.

11.5.3 Exploratory Objectives Analyses

11.5.3.1 Time to treatment failure

Time to treatment failure (TTF) is the time from randomization to the occurrence of discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. The treatment-failure date for patients who discontinue for reasons other than RECIST Version 1.1 (or RANO-BM criteria for CNS lesions in Part 2) progression will be the date of the last study drug administration. Patients who have not discontinued treatment prior to the data cut-off date will be censored at the date of last tumor assessment documenting no objective progression. TTF will be described by Kaplan-Meier methods and treatments will be compared using stratified log-rank test.

11.5.3.2 EORTC-QLQ outcomes

Analysis of the EORTC-QLQ-C30 questionnaires will be performed in accordance with the EORTC guidelines (Fayers, 2001). The subscales of the EORTC QLQ-C30 and the QLQ-LC13 will be scored based on the EORTC scoring manual. Scores will be standardized such that

higher scores on the EORTC QLQ-C30 or the QLQ-LC13 will represent higher ("better") levels of functioning and/or a higher ("worse") level of symptoms.

EORTC QLQ-C30 and QLQ-LC13 scale scores will be summarized by treatment group using descriptive statistics (mean, standard deviation, minimum, maximum and median) on ITT. An ANOVA model will be used to analyze the change in the EORTC QLQ-C30 and QLQ-LC13 scale scores from baseline to post-baseline visits.

For each QLQ-C30 and QLQ-LC13 subscale, the proportion of patients with improvement will be tabulated by treatment group and will be compared between treatment groups using a logistic regression model adjusting for the randomization stratification factors (region and platinum sensitivity).

Additional EORTC QLQ analyses will be performed and details are provided in a standalone PRO SAP.

11.5.3.3 Patient Global Impression of Change and Severity

The PGI-C and PGI-S will be used as anchors in analyses designed to compute a responder definition of the EORTC QLQ scales. This responder definition will be used in analysis of the specified EORTC QLQ-C30 and QLQ-LC13 scales as secondary endpoints.

11.5.3.4 EQ-5D-5L

EQ-5D-5L visual analog scale (VAS) will be descriptively reported as a total score. Utility score and change from baseline over time will be reported. Mean change scores will be compared between treatment groups descriptively and may be explored via longitudinal modeling (i.e., covariate analysis and repeated measures modeling).

11.5.3.5 Time to CNS Progression

The time to CNS progression is defined as the time from randomization to the development of CNS progression as defined by the RANO-BM working group (Lin, 2015). Time to CNS progression (by BICR and by investigator assessment) will be described by Kaplan-Meier methods and treatments will be compared using stratified log-rank test.

11.5.3.6 Biomarkers

The biobanked samples may be used to identify prognostic markers, as well as predictive markers (i.e, other variants of drug metabolizing enzymes such as UGT1A1, p53 mutations) that may correlate with the PKs, efficacy and safety of irinotecan liposome injection.

11.6 Safety Analysis

Safety analyses (AEs and laboratory analyses) will be performed using the safety population, defined as all patients receiving any study drug. Treatment assignment will be according to actual treatment received. Adverse events will be coded using MedDRA (Version 21.0 or later). Severity will be graded according to the NCI CTCAE Version 5.0.

Treatment-emergent adverse events are defined as any AEs reported from the date of first study drug exposure to 30 days after the last date of study drug exposure. Frequency and percentages of patients will be summarized for: any grade TEAE, Grade 3 or higher TEAE, study-drug related TEAE, serious TEAE, TEAE leading to dose modification, TEAE leading to study drug discontinuation, death and TEAE leading to death. Adverse events will be summarized by system organ class and preferred term. All AE data will be listed by patient. Based on accumulated data a subgroup analysis of safety by UGT1A1*28 allele status may be performed.

Laboratory data will be summarized according to parameter type. Where applicable, toxicity grading for laboratory safety parameters will be assigned based on NCI CTCAE Version 5.0 criteria.

11.7 Pharmacokinetic Analysis

11.7.1 Listings and Summary Statistics of Concentrations

Individual plasma concentrations for total irinotecan and SN-38 will be listed and summarized by timepoint and dose level, for both Part 1 and for Part 2, using descriptive statistics for continuous variables (number of available observations, number of below the limit of quantification (BLQ), mean, SD, %CV, geometric mean and $\%CV_{geomean}$, median, minimum, maximum).

11.7.2 Pharmacokinetic Data Analysis

Pharmacokinetics of total irinotecan and SN-38 will be quantified from the concentrations from plasma samples using nonlinear mixed effect modeling. The population PK model previously developed on historical data will be applied to this SCLC study by reassessing previous covariates found in the previous model and additional factors specific to this study if required. A full description of this Population PK analysis of the concentration data will be captured separately in a data analysis plan, and results will be reported in a standalone report.

11.7.3 Pharmacokinetics/Pharmacodynamics Relationship

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

12 STUDY ADMINISTRATION

12.1 Pre-Study Documentation

Prior to initiating the trial, the Investigator will provide the Sponsor or designee required documents according to ICH GCP, and at a minimum:

- A signed FDA Form 1572 or equivalent
- A current (i.e. updated no more than 12 months prior) curriculum vitae for the Principal Investigator and each sub-investigator listed on the FDA Form 1572 or equivalent that is signed and dated. A copy of the current medical license for the Investigator and each sub-investigator
- A letter from the IRB/EC stipulating approval of the protocol, the informed consent document, and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- The current IRB/EC membership list for the reviewing IRB/EC
- A signed Investigator Protocol Agreement
- A completed financial disclosure form for the Investigator and all sub-investigators
- A current laboratory certification for the local reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory.

12.2 Source Documents

The Investigator will maintain records separate from the case report forms in the form of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The Investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms when the

Sponsor's monitor visits the investigational site. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to enrollment in the study can be used to fulfill certain screening and baseline assessments. Source data must be attributable, legible, contemporaneous, original, accurate and complete. All information obtained from source documents will be kept in strict confidentiality. Source data sent to the Sponsor or the Sponsor's representative as supporting documentation for SAEs will be de-identified to preserve confidentiality.

12.3 Trial Ethics

The study will be performed according to the principles of the Declaration of Helsinki, the International Council on Harmonization guidance (ICH) on Good Clinical Practice and the requirements of the US FDA and/or local regulatory authorities regarding the conduct of human clinical trials

12.4 Patient Informed Consent

No study related procedures will be performed until a patient or a patient's legal representative has given written informed consent. The Sponsor will provide to the Investigator a sample informed consent document that includes all the requirements for informed consent according the ICH GCP, and all required local regulatory guidelines including applicable privacy laws. However, it is up to the Investigator to provide a final informed consent that may include additional elements required by the Investigator's institution. Changes to the Sponsor's sample informed consent should receive approval from the Sponsor or the Sponsor's representative prior to use in the study. The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the Investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the trial and who signs the informed consent form will be given a copy of the signed, dated and witnessed document. The provision of informed consent must be documented in the medical record.

The ICF will contain a separate section that addresses the use of all data and remaining material after analysis from mandatory samples and extra samples for optional future research. These data and biosamples may only be used for scientific health-related research to find new ways to detect, treat, prevent or cure health problems. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study and the storage period. A specific consent will be required to document a patient's agreement to allow any data and remaining specimens to be used for future research.

12.5 Investigational Review Board and Independent Ethics Committee Approval

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

This study has the option for patients to consent to the collection of samples for biobanking for future exploratory analysis, and storage for up to 15 years (where local regulations allow). A specific informed consent is required for the collection of these samples and will be explained after the patient has given written informed consent for the main study. Patients must receive an explanation that they are completely free to refuse to enter the exploratory part of the study and may withdraw from it at any time and for any reason up to 15 years after the end of the study and will still be allowed to take part in the main study.

12.6 Monitoring

Overall study monitoring will be conducted through a combination of on-site visit and centralized monitoring. Details regarding the monitoring will be described in the monitoring plan. A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. The Investigator will allow the Sponsor, and/or its representatives or designees, access to all pertinent medical records, as required by national regulations, in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process.

During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

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

In accordance with local regulations, such as the Health Insurance Portability and Accountability Act in the US and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

12.7 Data Quality Assurance

Electronic data capture will be utilised for collecting patient data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the e-signature of the person performing the action. This e-signature consists of an individual and confidential username and password combination. It is declared

to be the legally binding equivalent of the hand-written signature. Only sponsor authorised users will get access to the eCRF as appropriate to their study responsibilities. Site users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a service provider under the responsibility of the Sponsor's Data Management Department. All data management procedures will be completed in accordance with the Sponsor's and the CRO's Standard Operating Procedures.

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

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

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

The coding of an AE, medical history and concomitant medication terms will be performed by the service provider. Concomitant medications will be coded using the World Health Organisation Drug Dictionary and AEs/medical history terms will be coded using MedDRA.

12.8 Confidentiality

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

12.9 Protocol Amendments

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

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

12.10 Publication

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

The results of this study may be published or communicated to scientific meetings by the Investigators involved in the study. For multi-centre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted

for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

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

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

12.11 Records Retention

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

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

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

12.12 Study Termination

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

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns
- Drug supply or manufacturing issues
- The Sponsor's decision to modify or discontinue the development of irinotecan liposome injection in this indication
- A request to discontinue the study by the FDA and/or local regulatory authorities

The Sponsor will promptly inform all investigators and the FDA and/or local regulatory authorities if the study is suspended or terminated for any reason. The Investigator will promptly notify the IRB/IEC if the study is suspended or terminated.

13 INVESTIGATOR SIGNATURE PAGE

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

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

_____ _____

Signature of Investigator Date

_____

Print Name of Investigator

_____ _____

On behalf of the Sponsor Date

PPD

Oncology

Global Drug Development, R&D

IPSEN

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15 APPENDIX

15.1 Appendix I: Recommendations for Management of Chemotherapy Induced Diarrhea

Proposed algorithm for the assessment and management of treatment-induced diarrhea is provided below in Table 8. These guidelines are adapted from those developed by an American Society of Clinical Oncology (ASCO) panel and ESMO Clinical Practice Guidelines for treating chemotherapy-induced diarrhea (Benson 2004, Ustaris 2015, Bossi 2018). Also Section 5.3 for management of dose modifications.

Anti-diarrhea management should be initiated at the first episode of poorly formed or loose stools or the earliest onset of bowel movements that are more frequent than normal.

Table 8 Recommendations for Management of Chemotherapy Induced Diarrhea

Dietetic	
Dietetic Measures (applicable for all grades of diarrhea) Stop all lactose-containing products Drink 8 to 10 large glasses of clear liquids per day Eat frequent small meals Recommend low-fat diet enriched with bananas, rice, apple sauce and toast i.e. BRAT diet	
Fluid Intake Approximately 2L should be maintained Ensure appropriate fluid and electrolyte replacement	
Pharmacological Treatment	
First Line Therapy: loperamide	
Clinical Presentation	**Intervention**
If receiving prophylaxis:	Increase loperamide dose to a maximum of 16 mg/day. Continue until diarrhea free for 12 hours. If no improvement within 48 hours implement second-line therapy.
If new-onset diarrhea (i.e. first loose stool):	Take loperamide 4 mg with first bout of diarrhea followed by 2 mg every 4 hours or after every unformed stool (maximum 16 mg/day). Continue until diarrhea free for 12 hours. If no improvement within 48 hours implement second-line therapy.
With recovery to ≤Grade 1:	Take loperamide 4 mg one dose with each subsequent cycle of irinotecan liposome injection administration.
Second Line Therapy	
Grade 1 If persistent diarrhea on loperamide:	Add diphenoxylate, hydrochloride plus atropine suffate (Lotomil®) 2.5 mg every 6-8 hours. Monitor for trend in decreasing WBC and/or neutropenia. Recommend G-CSF if decreasing WBC and/or neutropenia to avoid infectious/septic complications. See Section 5.4.1.

Grade 2 If persistent diarrhea on loperamide:	Add octreotide (short acting) 150 µg subcutaneously tid or after initial dose of short acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg intramuscularly. Monitor for trend in decreasing WBC and/or neutropenia. Recommend G-CSF if decreasing WBC and/or neutropenia to avoid infectious/septic complications. See Section 5.4.1. Consider stool cultures to exclude infectious causes (e.g. Clostridium difficile) prior to prophylactic antibiotics, especially if diarrhea is persistent beyond 24 hours or if there is a fever or Grade 3 or 4 neutropenia
Grade 3/4 After intensive loperamide therapy:	Titrate loperamide to keep diarrhea controlled (<4 stools/day). Octreotide (100 to 150 µg subcutaneously bid or 25 to 50 µg/hour intravenously if dehydration is severe, with dose escalation up to 500µg subcutaneously tid). Intravenous fluids as appropriate. Consider prophylactic antibiotics, especially if diarrhea is persistent beyond 24 hours or if there is a fever or Grade 3 or 4 neutropenia. Stool cultures to exclude infectious causes. Monitor for trend in decreasing WBC and/or neutropenia. Recommend G-CSF if decreasing WBC and/or neutropenia to avoid infectious/septic complications. See Section 5.4.1. Consider stool cultures to exclude infectious causes (e.g. Clostridium difficile) prior to prophylactic antibiotics, especially if diarrhea is persistent beyond 24 hours or if there is a fever or Grade 3 or 4 neutropenia

15.2 Appendix II: ECOG Performance Status

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

a Published by Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.Am J Clin Oncol. 1982;5:649-655.

15.3 Appendix III: Response Criteria for CNS Metastases

Summary of the response criteria for CNS metastases proposed by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group (Lin, 2015)

	Complete Response	Partial Response	Stable Disease	Progressive Disease
Target Lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest diameter relative to nadira
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive diseasea
New lesion(s)b	None	None	None	Presenta
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicablec
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worsea
Requirement for response	All	All	All	Anyc

a Progression occurs when this criterion is met.
b A new lesion is one that is not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression.
c Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

15.4 Appendix IV: Temporary Measures and Procedures Related to COVID-19 Pandemic

This appendix serves as notification of the temporary measures put in place for the conduct of the study during the COVID-19 pandemic and until such time as the situation resolves, at which point the protocol assessments will return to those specified in the current approved protocol effective at that time. The timing of when the pandemic is declared over may vary on a country by country basis as well as between sites in the same country, and as such the temporary measures may remain in place for differing periods of time per country/site. Investigators will determine the feasibility of starting or continuing study treatment on a patient by patient basis, depending on the ability to conduct safety monitoring and providing patients an adequate supply of study treatment, in accordance with local requirements.

Any temporary measure will be reported as a protocol deviation related to COVID-19.

This appendix was assembled using suggestions from the TransCelerate publication "Beyond COVID-19: Modernizing Clinical Trial Conduct" published by TransCelerate Biopharma Inc. 2020, which was influenced by FDA and EMA guidance issued for conduct and management of clinical trials during the COVID-19 pandemic.

Specific Guidance for Study Visits and Assessments

Informed Consent (including Re-consent)

As per guidelines issued by the FDA in the US and in line with guidance in other countries, the use of electronic signatures is authorised to obtain the patient's informed consent. The Sponsor and IRB need to be notified, and approval obtained where applicable, of the use of electronic informed consent signature and the accepted electronic formats need to be clearly documented. This is not meant to replace the important discussion between the patient, Investigator and site staff. Such a discussion must still occur and be part of a screening visit (in-person, by telemedicine, or home health visit). A clear, documented process on how patients are contacted virtually to explain the study and close monitoring need to be in place.

Dosing visits (Arm A and Arm B)

Dosing visits may be delayed due to COVID-19 (for example temporary closure of the site, patient unable to travel etc). Dose delay rules should be followed per protocol (Section 6.2). In case of dosing visit delays outside of the protocol these should be discussed between the Investigator and the Sponsor. Screening visit and assessments (apart from informed consent as described above) must be performed on site.

Physical Examinations and ECOG Performance Status: Assessment can be done via telemedicine (as per the rules below) and should be done according to local practice.

Quality of Life Assessments:

The QoL assessments are routinely captured while the patient is at the site, in real time. The site has an electronic tablet containing the questionnaires, in which the patient records his/her answers. As some patients are concerned about touching the device, sanitation practices that allows for thorough cleaning of the device have been implemented. In cases where study staff are not allowed on site or patients unable to attend their visit, interview mode is used to capture e-PRO and electronic clinical outcome assessment (e-COA). The site staff will call the patient, ask the questions as per the assessment in exactly the same order and wording (paraphrasing is not allowed apart from the VAS scales for the EQ-5D-5L. The clinician should define for the patient the upper and lower bounds (ie. 100 is the best you you have ever felt and 0 is the worst)) and directly enter the data into the ePRO system on behalf of the patient. Answers to questions must not be noted down first and then entered into the eCRF as this could impact validation of

the ePRO tool. Details of the verification of the patient and the site personnel conducting the assessment should be documented.

The interview mode has been authorized by the vendor with specific guidance/rules provided to the sites to conduct these interviews.

Disease Evaluation: CT/MRI Scans: This study assessment does not always coincide with a dosing day, though it might coincide if the patient has had no dosing delays (e.g. due to toxicity). In the case where the assessment does not coincide with a dosing visit, to reduce the risk associated with travelling (to a study site), imaging may be performed at a local imaging facility. The modality to be used for the imaging is to be documented and shared with the local imaging facility for consistency to ensure the same imaging modality is used. Documentation of the imaging facility is to be collected by the site and retained. Scanned images are to be shared with the site. The site is responsible for submitting scans to the central imaging vendor. The RECIST reading is to be done by the Investigator (as per Section 8.8).

Sample Collection

Haematology and Biochemistry: To reduce the risk associated with travel to the site if the subject comes in the day prior to dosing for haematology sampling, or to reduce the risk associated with time the subject spends at the study site, a local laboratory may be used to obtain and analyse the haematology samples. Results of haematology samples taken need to be shared with the investigational site and assessed prior to dosing as per protocol requirements. Documentation of the local laboratory (accreditation and reference ranges) are required to be collected and shared with the Sponsor. As the subject comes at the site for dosing, effort should be made to collect biochemistry samples for central laboratory assessment, as well as all other central laboratory samples. If this is not possible, local biochemistry samples are to be collected as described above.

Pregnancy Test: Pregnancy testing is required on Day 1 of each cycle. To reduce the risk associated with travel to the site, if the patient comes in the day prior to dosing for pregnancy testing, or to reduce the risk associated with time the patient spends at the study site, a local laboratory, hospital or general medical practice may be used to obtain the pregnancy test. Results of the pregnancy test need to be shared with the investigational site and assessed prior to dosing as per protocol requirements.

Concomitant Medications and Procedures: Details can be collected by site staff via telephone call as per the rules relating to use of telemedicine below.

AE Reporting: Details can be collected by site staff via telephone call as per the rules relating to use of telemedicine below.

Specific Rules Relating to use of Telemedicine

The form of telemedicine used (phone call or use of a platform), the legal and privacy protection of the subject as well as details of the verification of the identity of the subject and site personnel conducting the assessment must be documented at site level and should be available for review by the monitor.

Note that further information about specific measures adopted for the COVID-19 situation to cover temporary discontinuations and SAE reporting are found in Sections 6.2.1 and 10.1.2, respectively.