SAP Title: A Phase 2, Multicenter, Open-label, Safety and Efficacy Study of XERMELO® (Telotristat Ethyl) plus First-line Chemotherapy in Patients with Locally Advanced, Unresectable, Recurrent **or** Metastatic Biliary Tract Cancer (BTC)

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TerSera Therapeutics LLC

LX1606.1-207-BTC

A Phase 2, Multicenter, Open-label, Safety and Efficacy Study of XERMELO® (Telotristat Ethyl) plus First-line Chemotherapy in Patients with Locally Advanced, Unresectable, Recurrent or Metastatic Biliary Tract Cancer (BTC)

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Final Statistical Analysis Plan

Version *2.0*

Prepared by:

PPD
929 North Front Street
Wilmington, NC 28401
and
TerSera
Therapeutics
LLC
520 Lake Cook
Road, Suite 500
Deerfield, IL
60015

PPD Biostatistics and Programming

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Author(s):

For PPD: CC1 CCI

<Client>: <Name>, <Title> <add more lines as required>

Approved by:

CCI CCI CCI

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Date *(DD-MMM-YYYY)*

CCI CCI CCI

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CCI CCI CCI

TABLE OF CONTENTS

SUMMARY OF CHANGES ..... **V**

LIST OF ABBREVIATIONS ..... **I**

1. INTRODUCTION **4**

2. OBJECTIVES **5**

2.1. Primary Objective *5*
2.2. Secondary Objective *5*
2.3. Exploratory Objective *5*
2.4. Pharmacokinetic Objective *6*
2.5. Substudy Objective *6*
2.6. Safety Objective *6*

3. INVESTIGATIONAL PLAN **6**

3.1. Overall Study Design and Plan 6
3.2. Study Endpoints 8
3.2.1 Primary Endpoint *8*
3.2.1.1 Primary Efficacy Endpoint 8
3.2.2 Secondary Endpoints *9*
3.2.3 Exploratory Endpoints *9*
3.2.4 Pharmacokinetic Endpoints *10*
3.2.5 Substudy Endpoints *10*
3.2.6 Safety Endpoints *10*
3.3. Treatments 11
3.4. Dose Adjustment/Modifications 12
3.4.1 Dose Modification – XERMELO *13*
3.4.2 Dose Modification – Cisplatin/Gemcitabine *13*
3.4.3 Clinical Stopping Rules *14*

4. GENERAL STATISTICAL CONSIDERATIONS **15**

4.1. Sample Size 16
4.2. Randomization, Stratification, and Blinding 17
4.2.1. Randomization and Stratification *17*
4.2.2. Blinding *17*
4.3. Analysis Population 17
4.3.1. Enrolled Population *17*
4.3.2. Per Protocol (PP) Population *18*
4.3.3. By Treatment Cycle Population *18*
4.3.4. Safety Population *18*
4.3.5. PK Population *18*

5. PATIENT DISPOSITION **18**

5.1. Disposition 18

5.2. PROTOCOL DEVIATIONS 19

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS 19

6.1. DEMOGRAPHICS 19
6.2. BASELINE DISEASE CHARACTERISTICS 20
6.3. MEDICAL HISTORY 20
6.3.1. General Medical History 20
6.4 INCLUSION AND EXCLUSION CRITERIA 21

7. TREATMENTS AND MEDICATIONS 22

7.1. PRIOR AND CONCOMITANT MEDICATIONS 22
7.1.1. Prior Medications 22
7.1.2. Concomitant Medications 22
7.2. CONCOMITANT PROCEDURES 23
7.3. STUDY TREATMENTS 23
7.3.1. Extent of Exposure 23
7.3.2. Treatment Compliance and Modifications 23

8. EFFICACY ANALYSIS 24

8.1. PRIMARY EFFICACY ANALYSIS 25
8.1.1 Progression-free Survival (PFS) 25
8.1.2 Sensitivity Analysis 27
8.2. SECONDARY EFFICACY ANALYSIS 27
8.2.1 PFS Rate at Month 12 and Median PFS 27
8.2.2 Overall Survival (OS) 28
8.2.3 Disease Control Rate (DCR) 28
8.2.4 Overall Response Rate (ORR) 28
8.2.5 Local Radiologist's Assessment (PFS, ORR, and DCR) 30
8.2.6 Change in Tumor Size 30
8.2.7 Sensitivity Analysis 30

9. EXPLORATORY ANALYSIS 30

9.1 Health-Related Quality of Life (HRQoL) 30
9.2 Subgroup Analysis 32
9.3 Sensitivity Analysis 32

10. SAFETY ANALYSIS 32

10.1. ADVERSE EVENTS 33
10.1.1. Incidence of Adverse Events 34
10.1.2. Treatment Emergent Adverse Events Summary by SOC and PT 34
10.1.3. Relationship of Adverse Events to Study Drug 35
10.1.4. Severity of Adverse Event 35
10.1.5. Adverse Events by Length of Exposure to Each Study Drug 36
10.1.6. Serious Adverse Events 36

10.1.7. Adverse Events Leading to Study Discontinuation *37*
10.1.8. Adverse Events Leading to Treatment Discontinuation *37*
10.1.9. Adverse Events Leading to Dose Reduction *37*
10.1.10. Adverse Events Leading to XERMELO Reduction *38*
10.1.11. Adverse Events Leading to XERMELO Interruption *38*
10.1.12. Adverse Events of Special Interest *39*
10.1.13. Deaths *39*
10.2. Clinical Laboratory Evaluations 39
10.2.1. Serum Albumin *40*
10.2.2. Pregnancy Test *40*
10.3. Vital Sign Measurements 40
10.4. Physical Examination 41
10.5. Electrocardiogram 41
10.6. Eastern Cooperative Oncology Group (ECOG) Performance Status 41
10.7. Depression Detection 41
10.8. Other Safety Data 42

11. PHARMACOKINETICS 42

12. PHARMACODYNAMICS 43

13. INTERIM ANALYSIS 43

14. REFERENCES 45

15. APPENDICES 46

15.1. Schedule of Study Procedures 46
15.2. Terms Considered Depression-related AESI, if Clinically Significant 51
15.3. Imputation 52
15.4. EORTC QLQ – BIL21 54
15.5. Visit Cycles and Analysis Timepoints 56
15.6. Detailed Summary of SAP Changes 58

Summary of Changes

Statistical Analysis Plan Revision History

Version	Date	Summary of Changes
2.0	03Feb2021	Updated according to new protocol amendment dated on 23NOV2020 and instruction from TerSera.

List of Abbreviations

1L	first-line
2L	second-line
5-HIAA	plasma 5-hydroxyindoleacetic acid
5-HT	serotonin
AE	adverse event
ALKP	alkaline phosphatase
ALT	alanine aminotransaminase
ANC	absolute neutrophil count
AST	aspartate aminotransaminase
AUC	area under the plasma concentration-time curve
$AUC_{(0-6)}$	AUC from time zero to 6 hours after dose administration
$AUC_{(0-last)}$	AUC from time zero to time of last measurable concentration
BICR	blinded independent central review
BLQ	below the limit of quantification
BMI	body mass index
BTC	biliary tract cancer
C1	Cycle 1
C1D1	Cycle 1, Day 1; Baseline (Baseline value is defined as the last non-missing data on or before the first dose of the study drug, unless otherwise specified)
C10D1	Cycle 10 Day 1 is intended as Month 6
C19D1	Cycle 19 Day 1 is intended as Month 12
CA 19-9	serum carbohydrate antigen 19-9
CCA	cholangiocarcinoma
CEA	carcinogenic embryonic antigen
CI	confidence interval
cis	cisplatin
cis/gem	cisplatin/gemcitabine: cisplatin 25 mg/m^2 administered intravenously (iv) over 90 minutes followed by gemcitabine iv 1000 mg/m^2 administered iv over 30 minutes (also referred to as 1L therapy)
CMP	complete metabolic profile
C_{max}	observed maximum plasma concentration
CR	complete response
CRF	case report form
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events (v5.0)
C_{trough}	trough plasma concentration (predose concentration)
CV	coefficient of variation
DCR	disease control rate defined as CR+PR+SD
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End-of-Study

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EOT	End-of-Treatment
FDA	United States Food and Drug Administration
GBC	gall bladder carcinoma
gem	gemcitabine
HDL	high-density lipoprotein
HEENT	head, ears, eyes, nose, throat
HRQoL	health-related quality of life
IHC	immunohistochemical
INR	international normalized ratio
iv	intravenously
Kel	apparent first-order terminal rate constant
KM	Kaplan-Meier
LDL	low-density lipoprotein
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NCS	not clinically significant
ORR	objective response rate defined as CR+PR
OS	overall survival
PD	progressive disease
PE	physical examination
PFS	progression-free survival
PK	pharmacokinetic
PP	Per Protocol Population
PR	partial response
PT	Preferred Term or prothrombin time
PTFP	post-treatment follow-up period
QLQ-BIL21	Cholangiocarcinoma and Gallbladder Cancer Module
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	quality of life
QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RS	raw score
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease or standard deviation
SFP	survival follow-up period
SOC	System Organ Class
SSAs	somatostatin analogs
t1/2	apparent terminal elimination half-life
TEAE	treatment-emergent adverse events
tid	3 times daily
t_{max}	time of maximum observed plasma concentration
TPH	tryptophan hydroxylase

TPH-1	tryptophan hydroxylase-1
TPR	time point response
v	version

1. Introduction

This Statistical Analysis Plan (SAP) describes the analysis and the data presentations to be applied to data gathered for Protocol No. LX1606.1-207-BTC to assess the safety, tolerability, and efficacy of XERMELO® (telotristat ethyl) plus first-line chemotherapy in patients with locally advanced, unresectable, recurrent or metastatic biliary tract cancer (BTC).

Collectively, BTC is a group of malignancies that arise from the epithelium of the biliary tract and includes cholangiocarcinoma (CCA) and gall bladder carcinoma (GBC). Management of risk factors and early detection of are key to improving survival in patients with BTC. These tumors are very aggressive malignancies with a very poor prognosis. The rarity of the disease limits the evidence to support role of adjuvant therapy. The available treatment options are also not sufficient to address the poor survival rates in patients with locally advanced, recurrent, or metastatic BTC.

For patients presenting with unresectable BTC (locally advanced, recurrent, or metastatic) the current standard first-line (1L) therapy is a combination of cisplatin (cis) and gemcitabine (gem). While there are studies showing that combination treatment (cis/gem) is superior to gemcitabine alone as 1L therapy, treatment options for patients with unresectable BTC following the failure of 1L therapy remain limited and are not supported by Phase 3 data.

In February 2017, the US Food and Drug Administration (FDA) approved the oral drug telotristat ethyl (XERMELO) as a second-line (2L) therapy to be used in combination with somatostatin analogs (SSAs) to help address inadequate control of diarrheal symptoms in patients with carcinoid syndrome (CS). While XERMELO is indicated for the treatment of CS diarrhea in combination with SSA therapy in adults inadequately controlled by SSA therapy, its mediation of serotonin (5-HT) may provide a larger benefit. A novel treatment approach that inhibits 5-HT production may provide clinical benefit to the significant number of patients with unresectable BTC. Adding a tryptophan hydroxylase (TPH) inhibitor, like XERMELO to the treatment paradigm in combination with 1L therapy, may improve the physician's armamentarium and fulfill the unmet medical need for patients with advanced BTC.

This study is intended to assess the safety and the effect of XERMELO in combination with 1L chemotherapy on progression-free survival (PFS) in patients with locally advanced, unresectable, recurrent or metastatic BTC who are naïve to tumor-directed therapy in the locally advanced or metastatic setting and for which treatment with 1L therapy is planned.

2. Objectives

2.1. Primary Objective

The primary objective of the study is to assess the safety and efficacy (PFS rate at Month 6) in the Safety population receiving the combination of XERMELO plus 1L treatment with cis/gem combination chemotherapy. Efficacy (PFS rate at Month 6) will also be evaluated in the Per Protocol Population (PP) and by treatment cycle.

2.2. Secondary Objective

To assess the effect of study treatment on the following:

- Overall survival (OS)
- OS rate at Months 6 and 12
- PFS rate at Month 12 and median PFS
- Disease control rate (DCR); defined as complete response (CR) + partial response (PR) + stable disease (SD) at Months 6, 12 and End-of-Study (EOS)
- Objective response rate (ORR) defined as CR + PR at Months 6, 12 and EOS
- Local radiologist's assessment of PFS, ORR, and DCR
- Change from Baseline in plasma 5-hydroxyindoleacetic acid ([redacted] at Months 6, 12 and EOS
- Change from Baseline in body weight at Months 6, 12 and EOS
- Change from Baseline in serum albumin at Months 6, 12 and EOS

Note: Unless otherwise indicated, all radiologic endpoints will be based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as determined by blinded independent central review (BICR).

2.3. Exploratory Objective

To assess the effect of study treatment on the following:

- Changes in health-related quality of life (HRQoL) as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Cholangiocarcinoma and Gallbladder Cancer (QLQ-BIL21) items from Baseline, at Months 6 and 12
- Change from Baseline in carcinogenic embryonic antigen (CEA) fragment at Months 6, 12 and EOS
- Subgroup analyses of PFS, OS, ORR, and DCR using both BICR and local radiologist's assessment, based on categorical group of Baseline and change from Baseline in:

[redacted]

  - body weight
  - serum albumin

  - correlation between Baseline neutrophil:lymphocyte ratio and OS
- Subgroup analyses in:
  - Patients with changes in liver function tests
  - Patients with Biliary stents
  - Location of disease (intrahepatic, extrahepatic , or gallbladder)
  - prior therapy
  - ECOG performance status
- Efficacy analysis by treatment cycle population.

2.4. Pharmacokinetic Objective

The pharmacokinetic (PK) of XERMELO and the active metabolite, LP-778902 will be characterized, where possible, when dosed as a combination treatment with cisplatin and gemcitabine. In addition, where possible, intrinsic and extrinsic factors contributing to variability in exposure of XERMELO and the active metabolite, LP-778902, might be explored.

2.5. Substudy Objective

- To assess the effect of study treatment based on characterization of tumor tissue by immunohistochemical (IHC) staining (ie, 5-HT and tryptophan hydroxylase-1 [TPH-1])
- To determine the population PK profile among patients who participate in intensive PK sampling
- The population PK modeling objective is outside the scope of this analysis plan; it will be performed by a different vendor and submitted as a separate report.

2.6. Safety Objective

Evaluation of overall safety will be assessed by means of the following:

- Incidence of treatment-emergent adverse events (TEAEs) and severity assessment using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
- Change from Baseline in clinical laboratory results including frequency of values meeting NCI CTCAE Grades >1, laboratory data toxicities as defined by NCI CTCAE v5.0, physical examination (PE) findings, vital signs, and electrocardiogram (ECG) findings

3. Investigational Plan

3.1. Overall Study Design and Plan

This study is a multicenter, open-label, 2-stage study to assess the safety, tolerability, and efficacy of XERMELO in combination with 1L therapy (cisplatin plus gemcitabine) in patients with unresectable, locally advanced, recurrent or metastatic BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer), who are naïve to tumor-directed therapy in the locally advanced or metastatic setting, and for which treatment with 1L therapy (defined as a combination of cis/gem) is planned.

The study involves: Screening, Treatment Period with Stages 1 and 2, Post-treatment Follow-up Period (PTFP), and Survival Follow-up. The schedule of events to be performed from Screening to End-of-Study (EOS) is presented in Appendix 15.1.

Prior to the conduct of any study-related screening procedure, written consent is to be obtained from all patients. The collection of serious adverse events (SAEs) will begin after the patient has signed the informed consent.

Stage 1 enrollment will include a Safety Run-in cohort. Safety and tolerability data will be evaluated for the first 6 patients who complete at least 21 days of safety follow-up after the first dose of combination treatment. Safety and tolerability data will be evaluated by the Coordinating Investigators, Sponsor, and Medical Monitor in accordance with established clinical stopping rules as described in Section 3.4. The evaluation will include all safety assessments from all patients obtained prior to the second chemotherapy cycle of the 6th patient enrolled. During this safety evaluation, Stage 1 enrollment will continue as per the study schema as described in Section 3.3. It is anticipated that a total of 20 patients will participate in Stage 1. If there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug, and if 12 or more (≥60%) of the 20 patients enrolled who are deemed responder, enrollment will continue to Stage 2.

Stage 2 may initiate enrollment once Stage 1 enrollment has been completed, in the absence of significant or unresolved Grade 3 or higher toxicities considered related to the study drugs. Approximately 33 additional patients are anticipated to participate in Stage 2. Study assessments in this stage will be identical to Stage 1.
From a total of 53 accrued patients from Stage 1 + Stage 2, if 34 (>60%) or more responses are observed (i.e., patients are alive and progression-free at Month 6) in the Safety population, the study will be declared successful. Efficacy will also be assessed in the PP population and by treatment cycle population.

All patients are expected to be followed for a total duration of 24 months after the Treatment Period, unless they prematurely discontinue or voluntarily withdraw consent from future study visits or assessments. This 24-month phase is divided into 2 periods; the Post-treatment Follow-up Period (PTFP) and the Survival Follow-up Period.

All patients are expected to enter PTFP at the time progressive disease (PD) is confirmed locally, or the patient is no longer able to tolerate chemotherapy plus XERMELO in the absence of PD. During the Post-treatment Follow-up Period, patients may continue treatment

with XERMELO at the discretion of the treating physician. Patients will complete scheduled study visits every 3 months for a total duration of 24 months, or until the patient begins a new tumor-directed therapy, declines further treatment after progression, prematurely discontinue, or withdraws consent from future study visits or assessments. At this time, the End-of-Study (EOS) procedures should be performed and the patient should enter the Survival Follow-up Period (unless 24 months of follow-up after the last dose of chemotherapy has already occurred).

Once a new tumor-directed therapy begins, or the patient declines further treatment after progression, the patient enters the Survival Follow-up Period. During this period, all patients (or caregivers, where appropriate) will be contacted by phone every 3 months to obtain the patient's survival status until death, prematurely discontinue, withdrawal of consent, loss to follow-up, or for a period of 24 months following the last dose of chemotherapy, whichever occurs first. The site should make every attempt to document the date of death, if appropriate.

Note: Patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

Note: Patients who enter SFP without entering or completing PTFP and who entered SFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

3.2. Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint of the study is to assess the safety, tolerability and efficacy of XERMELO in combination with cisplatin (cis) plus gemcitabine (gem).

3.2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS rate at Month 6, where patient disease progression is defined as the time from first dose date until the first determination of PD by central radiologic reading using RECIST v1.1 (Eisenhauer, 2009) or death from any cause.

3.2.2 Secondary Endpoints

The secondary efficacy endpoints include:

- OS
- OS rate at Months 6 and 12
- PFS rate at Month 12 and median PFS at Month 12
- DCR defined as CR + PR + SD at Months 6, 12 and EOS
- ORR defined as CR + PR at Months 6, 12 and EOS
- Local radiologist's assessment of PFS, ORR and DCR
- Change from Baseline in CCI CCI
- Change from Baseline in body weight at Months 6, 12 and EOS
- Change from Baseline in serum albumin at Months 6, 12 and EOS

3.2.3 Exploratory Endpoints

Note: Unless otherwise indicated, all radiologic endpoints will be based on RECIST v1.1 as determined by BICR.

To evaluate the effect of XERMELO when used in combination with 1L therapy, the following exploratory efficacy endpoints will be assessed:

- Changes in HRQoL as measured by EORTC QLQ-C30 and QLQ-BIL21 items at Baseline, Months 6 and 12
- Change from Baseline in CEA fragment at month 6, 12 and EOS
- Subgroup analysis of PFS, OS, ORR, and DCR using both BICR and local radiologist's assessment based on categorical group of Baseline and change from Baseline in:

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  - body weight
  - serum albumin
  - correlation between Baseline neutrophil:lymphocyte ratio and OS
- Subgroup analyses in:
  - Patients with changes in liver function tests
  - Patients with Biliary stents
  - Location of disease (Histology: intrahepatic, extrahepatic , or gallbladder)
  - prior therapy
  - ECOG performance status
- Efficacy analysis by treatment cycle (such as in patients who completed CCI CCI CCI with combination treatment.

3.2.4 Pharmacokinetic Endpoints

For patients with intensive PK assessments on Cycle 1 Day 1 and Cycle 1 Day 8, the following plasma PK parameters will be estimated by non-compartmental analysis, where possible, for XERMELO and its active metabolite LP-778902. Additionally, trough plasma concentration (C_{trough}) values for additional cycles will be reported for all patients to the extent data are available.

Table 1 Pharmacokinetic Parameters

PK Parameter	Definition
C_{max}	observed maximum plasma concentration
C_{trough}	trough plasma concentration (predose concentration)
t_{max}	time of maximum observed plasma concentration
$AUC_{(0-6)}$	area under the plasma concentration-time curve from time zero to 6 hours after dose administration.
$AUC_{(0-last)}$	area under the plasma concentration-time curve from time zero to time of last measurable concentration
Kel	apparent first-order terminal rate constant
t½	apparent terminal elimination half-life

3.2.5 Substudy Endpoints

One substudy is conducted in parallel to the main study. The endpoint of this study is the characterization of the tumor tissue by IHC staining (ie, 5-HT and TPH-1) at Baseline among patients in whom tissue samples are available.

3.2.6 Safety Endpoints

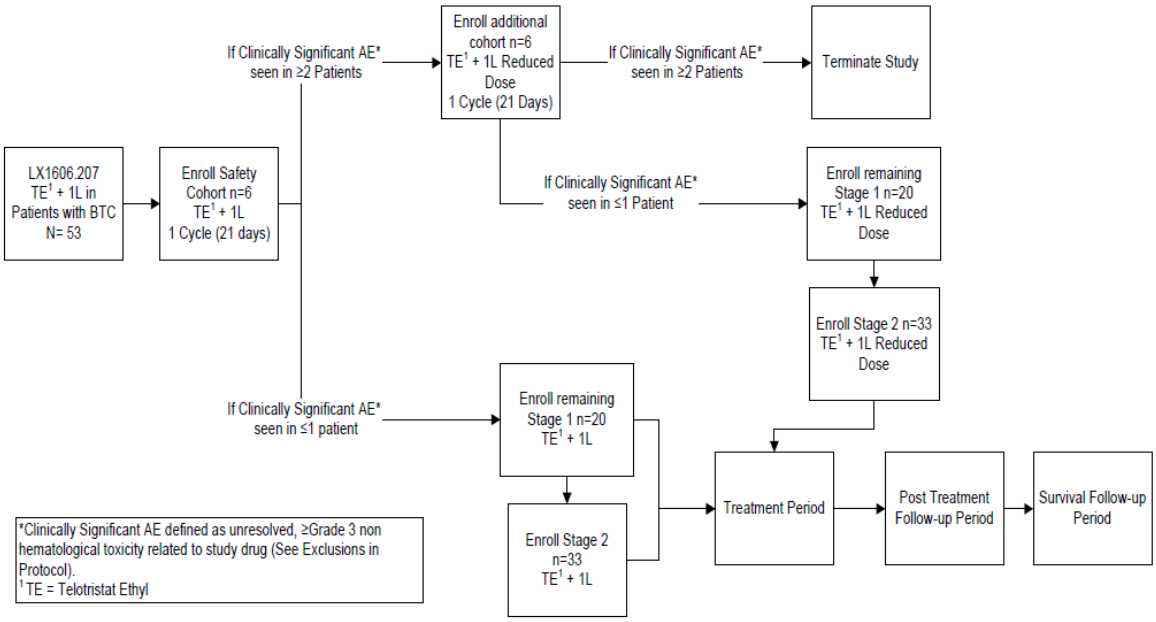
Safety endpoints are as follows:

- Incidence of TEAEs, TEAEs by severity, TEAEs by relationship to each of the study drugs, TEAEs by study drugs exposure time, TEAEs leading to discontinuation from the study, TEAE leading to dose reduction, TEAE leading to XERMELO reduction, TEAE leading to XERMELO interruption, TEAE leading to discontinuation from treatment, SAEs, and deaths
- Actual and change from Baseline in clinical laboratory results including frequency of values meeting NCI CTCAE Grades >1, laboratory data toxicities as defined by NCI CTCAE v5.0
- Actual and change from Baseline in vital signs results
- Actual and change from Baseline in PE findings
- Actual and change from Baseline in 12-lead ECG findings

3.3. Treatments

The treatment schema is summarized in Figure 1.

Figure 1 Treatment Schema



In both Stages 1 and 2, study treatment is administered to patients in the following manner:

1) On Day 1 (D1), eligible patients are to initiate Cycle 1 (C1), a 21-day cycle of XERMELO plus 1L therapy (herein referred to as "combination treatment") as follows:
   - XERMELO 250 mg (1 x 250-mg tablet) given as an oral dose 3 times daily (tid) for 7 days, plus
   - Cisplatin 25 mg/m^2 administered intravenously (iv) over 60 to 90 minutes, followed by
   - Gemcitabine 1000 mg/m^2 administered iv over 30 minutes
2) On Day 8, patients receive combination treatment as follows:
   - XERMELO 500 mg (2 x 250-mg tablet) tid for 14 days, plus
   - Cis/gem as described above
3) Every 21 days thereafter, patients initiate a new 21-day cycle (eg, Cycle 2 [C2], Cycle 3 [C3]) and receive combination treatment, administered as:
   - XERMELO 500 mg tid, plus
   - Cis/gem as described above on Day 1 and Day 8 of each cycle

Patients are expected to undergo approximately 6 months of combination treatment.

Note: Patients may continue to receive treatment for as many cycles possible, until progressive disease (PD) (up to 19 cycles during the Treatment Period), and during the Post Treatment Follow-up Period (up to an additional 24 months) at the discretion of the Investigator.

Dose modification(s) and/or delay in treatment may be permitted as described in Section 3.4. During the Treatment Period, patients may discontinue cisplatin and continue treatment with XERMELO plus gemcitabine alone at the Investigator's discretion. Gemcitabine should be administered on the same schedule as described above.

Patients may continue to receive combination treatment as described above for as many cycles as possible until PD as determined by local review, unacceptable toxicity, prematurely discontinue, or the patient withdraws from treatment. At this time, chemotherapy is discontinued, the End-of-Treatment (EOT) assessments should occur, and the patient should enter the PTFP. Visit dates for Follow-up period are based off the EOT date. During PTFP, patients may continue treatment with XERMELO at the discretion of the treating physician.

3.4. Dose Adjustment/Modifications

Dose modification(s) and/or delay in treatment may be permitted as described in Sections 3.4.1 and 3.4.2. Section 3.4.3 describes the clinical stopping rules during Stage 1 Safety Run-in of the Treatment Period.

For the purposes of this study, the following definitions apply:

- **Interruption:** temporary stoppage of 1 or both treatments of the assigned combination treatment (XERMELO and/or 1L) but then resuming the treatment(s) within 3 weeks for XERMELO or at the next treatment cycle for 1L chemotherapy
- **Discontinuation:** prematurely discontinue or prematurely withdrawal from 1 or both treatments of the assigned combination treatment (XERMELO and/or 1L) defined as a dose interruption lasting for >3 weeks (XERMELO) or a missed cycle (cis/gem). Note, however, that discontinuation of cisplatin, but continuation of treatment with gemcitabine alone, will not be classified as discontinuation.

If gemcitabine is deferred, cisplatin will also be deferred. Day 8 treatment may be deferred for toxicity reasons by 1 week only. If a second deferral is needed, the treatment will be omitted, and the patient will move on to the next treatment cycle.

3.4.1 Dose Modification – XERMELO

In general, the following dose modification rules will be used with respect to potential toxicity and management of TEAEs believed to be related to XERMELO. Toxicity will be assessed according to the NCI CTCAE v5.0.

Table 2 Toxicity Grade of TEAE and Corresponding XERMELO Dosing Action

Grade of Event	Management/Next XERMELO Dose[1]
Grade 1	No change in dose
Grade 2	Hold until ≤Grade 1. Resume at same dose level.
Grade 3	Hold until ≤Grade 1. Resume at 1 dose level lower (250 mg tid).[2]
Grade 4	Discontinue treatment

[1]Rechallenge may be permitted upon consultation with the Medical Monitor.
[2]Patients unable to tolerate 250 mg tid should be discontinued from XERMELO.

The details on recommended management of specific adverse events (AEs) are presented on Section 7.5.1 of the Protocol.

3.4.2 Dose Modification – Cisplatin/Gemcitabine

In general, CCI CCI CCI CCI CCI CCI
Toxicity will be assessed according to the NCI CTCAE v5.0.

Table 3 Dose Reduction

Dose Level	Gemcitabine	Cisplatin
Starting Dose	1000 mg/m^2	25 mg/m^2
Reduced Dose	800 mg/m^2	20 mg/m^2

The following tables show the dose modification rules that will be used with respect to hematologic/nonhematologic toxicity on Day 1/8 of each treatment cycle believed to be related to cisplatin or gemcitabine.

Table 4 Dose Reduction for Hematologic Toxicity on Day 1

ANC		Platelet Count	Gemcitabine/Cisplatin
≥1,000/mm^3	and	≥100,000/mm^3	Treat as scheduled
<1,000/mm^3	or/and	<100,000/mm^3	Defer treatment by 1 week. Reduce dose by 1 level for next treatment.

Table 5 Dose Reduction for Hematologic Toxicity on Day 8

ANC		Platelet Count	Gemcitabine/Cisplatin
≥1,000/mm^3	and	≥75,000/mm^3	Treat as scheduled
<1,000/mm^3	or/and	<75,000/mm^3	Defer treatment by 1 week. Reduce dose by 1 level for next treatment. If a second deferral is needed, treatment will be omitted.

Table 6 Dose Reduction for Nonhematologic Toxicity on Day 1

Nonhematologic Toxicity[1]	Gemcitabine/Cisplatin
Grade 1 or 2	Treat as scheduled
Grade 3 or 4	Defer treatment until resolves to ≤Grade 1. Reduce dose by 1 level for next treatment.

[1]Permissible exceptions to this rule are Grade 3 nausea, vomiting, hypertension, diarrhea, constipation, and transient electrolyte abnormalities that resolve within 72 hours following institution of appropriate supportive care and alopecia.

Table 7 Dose Reduction for Nonhematologic Toxicity on Day 8

Nonhematologic Toxicity[1]	Gemcitabine/Cisplatin
Grade 1 or 2	Treat as scheduled
Grade 3 or 4	Defer treatment until resolves to ≤Grade 1. Reduce dose by 1 level for next treatment. If deferral is needed for more than 1 week, treatment will be omitted.

[1]Permissible exceptions to this rule are Grade 3 nausea, vomiting, hypertension, diarrhea, constipation, and transient electrolyte abnormalities that resolve within 72 hours following institution of appropriate supportive care and alopecia.

3.4.3 Clinical Stopping Rules

The rules described below will include all safety assessments for all patients obtained prior to the second chemotherapy cycle of the 6th patient enrolled. The subsequent approach will be followed:

- If ≤1 patient has a clinically significant (CS) AE, the study will continue without a dose adjustment.
- If ≥2 patients have a CS AE, the dose level will be decreased to the Reduced Dose level in accordance with Table 7, and 6 additional patients will be enrolled and treated at the Reduced Dose level for 1 full cycle.
  - If ≤1 patient has a CS AE at the Reduced Dose level for the 1st cycle, the Reduced Dose level will be used for the study.
  - If ≥2 patients have a CS AE at the Reduced Dose level, the study will be stopped.

Note that a CS AE is considered an unresolved ≥Grade 3 nonhematological toxicity, which is related to the study drugs, excluding: controllable nausea, vomiting, hypertension, diarrhea, constipation, transient electrolyte abnormalities, and alopecia; Grade 3 or higher febrile neutropenia.

Table 8 Safety Run-in Dose Reduction

Dose Level	Gemcitabine	Cisplatin	XERMELO
Starting Dose	1000 mg/m^2	25 mg/m^2	500 mg tid
Reduced Dose	800 mg/m^2	20 mg/m^2	250 mg tid

Note that if a patient experiences a Grade 4 toxicity during the Safety Run-in, the Sponsor, in consultation with the Investigator, will determine if additional patients should be enrolled at the Reduced Dose level.

4. General Statistical Considerations

Continuous data will be summarized using descriptive statistics (ie, n, mean, standard deviation (SD), median, minimum and maximum). For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median and 95% confidence intervals (CIs) will be displayed to 1 level of precision greater than the data collected. Standard deviation will be displayed to 2 levels of precision greater than the data collected.

Categorical variables will be summarized descriptively by their counts and associated percentages. The denominator for all percentages will be the number of patients within the combination treatment for the population of interest, unless otherwise stated. Percentages will be presented to 1 decimal place. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values.

Baseline value is defined as the last non-missing data on or before the first dose of the study drug, unless otherwise specified.

For the purpose of statistical analyses, Cycle 10 Day 1 is intended as Month 6, and Cycle 19 Day 1 is intended as Month 12.

All summaries will be reported by study time point, as applicable.

Demographic data, Baseline disease characteristics, prior and concomitant medications, treatment compliance, treatment exposure, AE, laboratory tests, vital signs, PE findings, 12-lead ECG findings, and final disposition will be summarized descriptively. In addition,

shift table analyses will be applied to the laboratory data. No statistical tests will be performed. Analyses will be based on the Safety population.

The primary and secondary efficacy endpoints will be analyzed based on the Safety population. Additional analyses for the primary and secondary efficacy endpoints will be performed using the PP population.

For PFS and OS, the Kaplan-Meier (KM) method will be used to estimate the survival function. The distribution of PFS and OS will be used to estimate the survival rates and corresponding 95% CI at Month 6 and Month 12. Patients without PD or death will be censored at the last adequate confirmed radiographic assessment by the central reviewers prior to the study completion, date of discontinuation from the study, date of discontinuation from the treatment (if there is no 6-month assessment) or the start date of new line of anticancer treatment.

Subgroup analyses may be performed based on the primary tumor site, prior therapy(ies), performance status, major demographic and prognostic subgroups, extent of disease, and Baseline biomarker levels.

For binary endpoints estimated as binomial proportions, such as ORR and DCR, the frequency and proportion of patients assessed as responder and non-responder as an outcome will be presented at each assessed study time point.

Other efficacy endpoints will be summarized descriptively by study time point. Change from Baseline for CCI CCI CCI will be summarized descriptively and 1-sample t-tests may be performed to test for significance using a 5% level of significance.

All data values will be provided in listings.

During the programming period, the table/listing/figure shell format and footnote might be edited. And this kind of change is not be considered as analysis changes or impact the analysis results.

4.1. Sample Size

The sample size was computed by satisfying design assumptions for the primary efficacy endpoint of the study; which is to assess the PFS responder rate at Month 6.

Month 6 PFS responder rates of 70% and 55% are assumed for the XERMELO arm and historical control arms, respectively. Simon's 2-stage optimal design (Simon, 1989) is used to test these rates. The null hypothesis, that the true response rate is p_0=0.55, will be tested

against a 1-sided alternative. In the first stage, n_1=20 patients will be accrued. If there are r_1=11 or fewer responses in these n_1=20 patients, the study will be stopped. Otherwise, 33 additional patients will be accrued for a total sample size of n=53. The null hypothesis will be rejected if r_2= 33 + 1 or more responses are observed in 53 patients. This design yields a Type I error rate = 0.097 and statistical power = 0.802 when the true response rate is p_1= 0.70.

In the Stage 1 Safety population, if there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and if 12 (60%) or more of the 20 patients enrolled who are deemed responders per the definition in Section 8.1.1 after the 20th patient is censored, is alive and progression-free at the Month 6 assessment in the Safety Population, enrollment will continue to Stage 2.

The target sample size of 53 patients is expected to be accrued over a period of 18 months, with the last enrolled patient followed for 6 months after the start of receiving study treatment. Under an exponential sampling process, the median follow-up time for the time-to-event endpoints (eg, PFS, OS) will be 15 months.

4.2. Randomization, Stratification, and Blinding

4.2.1. Randomization and Stratification

Randomization and stratification are not applicable. This is a nonrandomized study. Eligible patients will be assigned to treatment once eligibility has been confirmed.

4.2.2. Blinding

Blinding is not applicable. This is an open-label study.

4.3. Analysis Population

The primary and secondary efficacy endpoints will be analyzed based on the Safety population. Additional analyses for the primary and secondary efficacy endpoints will be performed using the Per Protocol (PP) population.

4.3.1. Enrolled Population

The enrolled population will consist of those patients with informed consent date.

All listings and disposition tables will be based on the Enrolled population.

4.3.2. Per Protocol (PP) Population

The Per Protocol population will consist of those patients that [redacted] and who have no major protocol violation(s) that would interfere with the collection or interpretation of the efficacy data. Determination of the PP population will be made before database lock.

The analysis population will be used for analysis of primary and secondary efficacy endpoints.

4.3.3. By Treatment Cycle Population

The by treatment cycle population consist of all patients who completed [redacted] combination treatment.

The by treatment cycle population will be used for analysis of all efficacy endpoints as exploratory analysis as well as all AE outputs.

4.3.4. Safety Population

The Safety population will consist of all patients receiving any fraction of a dose of any of the study drugs (any of the study drug components).

The Safety population will be used for analysis of primary and secondary efficacy endpoints as well as safety endpoints.

4.3.5. PK Population

The PK population will consist of all patients treated with at least 1 dose of study drug and who have adequate samples taken to reliably estimate at least 1 of the PK parameters of interest. Determination of the PK population will be reviewed after all PK concentration data are made available.

This population will be used for estimation of PK endpoints.

5. Patient Disposition

5.1. Disposition

The number of patients enrolled in the study will be tabulated. Tables will indicate the number of patients who were enrolled into the study, the number of patients who completed the treatment period, the number of patients who completed the study, and the

number of patients who prematurely discontinued treatment period or study (early termination) for any of, but not limited to, the following reasons:

- Adverse event
- Protocol deviation
- Screen failure
- Lost to follow-up
- Withdrawal by patient (withdrawal of consent)
- Non-compliance
- Investigator's decision
- Study terminated by Sponsor (sponsor decision)
- Pregnancy
- Disease progression
- Suicidal ideation
- Death
- Other

All percentages will be based on the number of enrolled patients.

Patient disposition data will be presented in a listing.

5.2. Protocol Deviations

Protocol deviations will be presented in a listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

All baseline patient characteristics of demographics data will be presented for the Safety population. Demographic characteristics will be collected at Screening.

The following variables will be summarized:

1. Continuous baseline demographic variables:
    - Age at time of consent (years)
    - Height (in inches)
    - Weight (in kg)
    - BMI (in kg/m^2)
2. Categorical baseline demographic variables:
    - Age: <Median and ≥ Median age
    - Sex (male, female)
    - Childbearing potential (if female) (Yes, No)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race: All races (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other) and White vs Non-white

Patient demographics will be presented in a listing.

6.2. Baseline Disease Characteristics

Baseline values from the parameters below, but not limited to, will be tabulated:

- Eastern Cooperative Oncology Group (ECOG) performance status
- Cancer history information (Type of biliary tract cancer, histology, stage of cancer at study entry, duration of cancer at study entry, primary tumor location and metastases location)
- Patients with changes in liver function tests
- Patients with Biliary stents
- Prior therapy

Duration of cancer at study entry is defined as the date of inform consent minus the date of diagnosis + 1 and will be presented in months. Incomplete dates will be derived following the same rules for medical history.

Patients with changes in liver function tests will be identified using "Drug related hepatic disorders - comprehensive search" PT coding terms based on AE records. Patients with Biliary stents will be identified using “Biliary stent”, “Biliary Tract stent”, “Bile duct stent” from Medical history term. Patients with prior therapy will be identified using the leading question “Is Condition or Term associated with BTC?” in Medical history CRF page.

Baseline disease characteristics will be summarized in table and also will be presented in a listing. C1D1 images or images being obtained within 6 weeks prior to Day 1, or whichever images were closest in date to C1D1 are submitted to BICR for establishment of Baseline.

6.3. Medical History

6.3.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 or higher and actual version number will be denoted in the

outputs. The number and percentage of patients with any medical history at Baseline will be summarized overall and for each system organ class and preferred term. Percentages will be calculated based on number of patients in the Safety population. Incomplete dates will be imputed following rules in Section 15.3.

Patient medical history data including specific details will be presented in a listing.

6.4 Inclusion and Exclusion Criteria

Inclusion and exclusion data will be listed only for patients that did not meet inclusion/exclusion criteria.

6.5 Subgroups

The following subgroups will be defined:

- CCI
- body weight – Subgroup categories: <Median and ≥ Median baseline weight
- serum albumin - Subgroup categories: Normal and Abnormal baseline albumin

Demographics and disease characteristics will be considered as subgroups including:

- major demographic
  - Age: <Median and ≥ Median age
  - Sex: Male vs Female
  - Race: White vs Non-white
- Subgroup analyses in:
  - Patients with changes in liver function tests
  - Patients with Biliary stents
  - Location of disease (Histology: intrahepatic, extrahepatic, or gallbladder)
  - Prior therapy
  - ECOG performance status

Subgroups mentioned in the protocol based on correlation between Baseline neutrophil:lymphocyte ratio and OS, prognostic subgroups, extent of disease are not

planned but might be performed upon reviewing the data. Such analyses will be defined in the Clinical Study Report.

Patients with changes in liver function tests will be identified using "Drug related hepatic disorders - comprehensive search" PT coding terms based on AE records. Patients with Biliary stents will be identified using “Biliary stent”, “Biliary Tract stent”, “Bile duct stent” from Medical history term. Patients with prior therapy will be identified using the leading question “Is Condition or Term associated with BTC?” in Medical history CRF page.

Subgroup analyses of PFS, OS, ORR, and DCR will be evaluated for exploratory endpoints.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Information on prior and concomitant medications taken by patients are recorded in the electronic Case Report Form (eCRF). Incomplete dates will be imputed following rules in Section 15.3. All medications will be listed.

7.1.1. Prior Medications

Prior medications are defined as all medications and treatments taken prior to initiation of study medication. Any medications and treatments taken prior and not stopped prior to the first study medication will be counted in both prior medication and concomitant medication. The total number of prior medications and the number and percentages of patients with at least 1 prior medication will be summarized. The number and percentages of all prior medications will be summarized by drug class and preferred term. All summaries will be performed using the Safety population.

Medications will be coded using the WHODRUG 20180901 or higher and actual version number will be denoted in the outputs.

7.1.2. Concomitant Medications

All concomitant medications and other treatments taken during the study, including modifications to dosage and/or frequency, will be recorded in eCRF.

Information on concomitant medications will be summarized similarly to how prior medications will be summarized in Section 7.1.1.

7.2. Concomitant Procedures

The following patient information on prior surgeries or procedures will be presented in frequency tabulations:

- Number of patients with any prior surgeries or procedures
- Type of procedure (surgery, radiation therapy, chemotherapy, imaging, other)

Incomplete dates will be imputed following rules in Section 15.3.

Patient information on prior surgeries or procedures will be presented in a listing.

7.3. Study Treatments

Administration of XERMELO, gemcitabine, and cisplatin will be documented at each visit as described in Section 15.1.

7.3.1. Extent of Exposure

The treatment schema is discussed in detail in Section 3.3.

The following variables will be summarized by XERMELO, cisplatin and gemcitabine separately:

1. Continuous drug exposure variables:
    - **Duration of treatment exposure (days)** is defined as the total number of days a patient was exposed to the study drug. It will be calculated as (last dose date – first dose date + 1), where the first dose date is assumed to be Cycle 1 Day 1 for each drug.
    - **Cumulative dose (mg)** is defined as the sum of all doses taken per drug during the treatment period for XERMELO only based on drug accountability.
2. Categorical drug exposure variable:
    - Dosing status (dosed, not dosed) per cycle

Overall treatment duration and dose status will also be presented in the table.

Patient drug exposure will be presented in a listing.

7.3.2. Treatment Compliance and Modifications

Patients must maintain at least 75% compliance in dosing to be deemed as compliant. In the event of a missed or vomited XERMELO dose, patients will take their subsequent dose at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3-hour window for XERMELO should be considered missed. A dose delay of more than 1 week for cisplatin and gemcitabine should also be considered missed. Missed or vomited doses will not be made up.

The following variables will be summarized:

1. Continuous drug exposure variables:
    - Number of dose modifications per cisplatin and gemcitabine
    - Number of dose interruptions or missed doses per cisplatin and gemcitabine
    - **Compliance (%)** defined as [(actual number of tablets taken over the study period prior to EOT) / (designated total number of tablets that should have been taken over the study period prior to EOT)] * 100 for XERMELO. Actual number of tablets taken will be calculated using the dispensed and returned count from the XERMELO Dispensation CRF page. All the tablets not returned will be considered as taken by patient. Designated total number of tablets will be based on exact days patients were put under treatment cycles (250 mg tid starting on Day 1 and 500 mg tid staring on Day 8 in cycle 1 and 500 mg tid in cycle 2 and after) regardless dose interruptions and/or modifications.
2. Categorical drug exposure variable:
    - At least 1 dose modification (yes, no)
    - Reason for dose modification per cisplatin and gemcitabine
    - Reason for dose interruption per cisplatin and gemcitabine
    - Compliance category (<75%, ≥75%) for XERMELO

8. Efficacy Analysis

The primary and secondary efficacy endpoints will be analyzed based on the Safety population. Additional analyses for the primary and secondary efficacy endpoints will be performed using the PP population.

All imaging will be assessed by local radiologist and the BICR. The BICR will supersede the local radiologist's assessment for the purpose of primary efficacy analysis and all applicable key secondary objectives. A secondary analysis will be performed to further evaluate the primary and secondary efficacy endpoints using the local radiologist assessments.

PFS and OS will be summarized using Kaplan-Meier method in both summary tables and figures.

8.1. Primary Efficacy Analysis

8.1.1 Progression-free Survival (PFS)

Progression-free survival (PFS) will be defined as the time from first dose of study treatment until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of radiological disease progression, as assessed through the radiographic assessment by the central reviewers using RECIST version 1.1 (v1.1). Duration of progression-free survival (PFS) in days is defined as the time between the date of first dose of study drug and the date of the first occurrence of one of the following events:

- Radiological disease progression per RECIST v1.1 as assessed by the central reviewers
- Death due to any cause

For patients who do not experience one of these events by the time of data cutoff, PFS will be right censored at the date of last adequate disease assessment. An adequate disease assessment is a non-missing, valid scan where the overall assessment is defined by RECIST v1.1 criteria. For patients who do not experience disease progression, and do not have any adequate post-Baseline disease assessments, PFS will be right censored at first dose date. For patients who start a new line of anticancer treatment, PFS will be censored at the date of last adequate disease assessment prior to the start date of new line of anticancer treatment. If no such assessment is made, then censoring is applied on the first dose date. A Safety physician from TerSera will identify the anticancer treatments and first date of their administration from the concomitant medication records.

The full event and censoring rules for deriving PFS are specified in Table 9 below. Cycle 10 Day 1 is considered the Month 6 timepoint and Cycle 19 Day 1 is considered the Month 12 timepoint for analysis purposes. Patients who prematurely discontinued from Treatment Period or withdrew consent from Treatment Period prior to Month 6 of the Treatment Period, will be asked to reconsent to allow for images and or imaging reports, obtained locally, to be submitted to BICR.

Table 9 Censoring Conventions for PFS

Situation	Date of Progression or Censoring	Outcome
Disease progression	Date of scan confirming progression	Event
Disease progression documented from an assessment made after missing 2 or more consecutive scheduled radiological assessments	Latest of: ➢ Last adequate disease assessment prior to the missing 2 or more consecutive scheduled radiological assessments ➢ The first dose date	Censored
Death	Date of death	Event
Death after missing 2 or more consecutive scheduled radiological assessments	Latest of: ➢ Last adequate disease assessment prior to the missing 2 or more consecutive scheduled radiological assessments ➢ The first dose date	Censored
Treatment discontinuation for toxicity or other reasons (except death) prior to disease progression and Month 6 radiological assessment is not available	Latest of: ➢ Last adequate disease assessment ➢ The first dose date	Censored
No death and no disease progression after first dose date	Latest of: ➢ Last adequate disease assessment ➢ The first dose date	Censored
Start a new line of anticancer treatment	Latest of: ➢ Last adequate disease assessment ➢ The first dose date	Censored

The primary efficacy endpoint is the PFS response rate at 6 months and scheduled cycle 10 day 1 disease assessment results will be used for this purpose. This is a binomial variable in which the numerator is derived as the number of patients at 6 months who are alive and event-free. Event-free means that a valid radiologic assessment of disease (ie, radiological scan of the tumor) at 6 months shows that the patient has no progressive disease (PD) per RECIST 1.1 criteria. Such patients will be classified as "successes" or "responders" for the PFS response rate outcome. This may apply to patients that dropped from the study before 6 months, but returned to the clinic and had a valid scan performed at the Month 6 visit. Patients with radiologic evidence of PD or who died from any cause before the 6-month assessment will be classified as "failures" or "non-responders". Patients lacking a valid radiologic assessment at Month 6, for any reason, will also be classified as "failures" or "non-responders". This includes patients stopping study treatment for any reason (eg, adverse event) and who do not return for the 6-month scan. Assessments made after initiation of a new line of anticancer treatment will be censored in the analysis, meaning that scans following such an initiation will not be valid to determine PFS

responder status for the study regimen. In cases that initiation of other anticancer treatments starts before the 6-month disease assessment, such patients will be classified as "failures" or "non-responders" in the analysis. The Safety population is used as the denominator in deriving the PFS rate.

In addition to the PFS response rate, the PFS rate at Month 6 derived as a function of a time-to-event outcome, and the corresponding 95% confidence interval (CI), will be presented. The Kaplan-Meier method will be used to estimate the survival function of this measure of the PFS variable.

In the first stage of Simon's 2-stage design, PFS tables and associated listings will be provided after 20 patients are accrued with Month 6 assessment results. If 12 or more of the 20 patients enrolled are deemed responders per the PFS response rate definition provided above, enrollment will continue to the maximum sample size of 53 patients. Observation of 11 or fewer PFS responders at the Stage 1 analysis will result in the termination of patient accrual. Should data show that, via routine trial monitoring, the number of patients reaching the 6-month disease assessment will not allow for a positive PFS result at either Stage of the design (eg, excessive number of patients discontinuing the study), consideration will be given to stop patient accrual at that time.

8.1.2 Sensitivity Analysis

Addition to original PFS definition, clinical disease progression can be also considered as evidence of disease progression when there is no supportive radiographic assessment of PD. The date of clinical/symptomatic disease progression assessed by the investigator will be used as the event date in a sensitivity analysis. It can be either the last dose date when the primary reason of study drug discontinuation is disease progression or study termination date when the primary reason for discontinuation is disease progression, whichever earlier. Also, PD or death after missing 2 or more consecutive scheduled radiological assessments is considered as an event in the sensitivity analysis. This sensitivity analysis will be based on the Safety population.

A separate sensitivity analysis will also be performed on the PFS response rate as defined in Section 8.1.1 based on the PP population as well as by treatment cycle population.

8.2. Secondary Efficacy Analysis

8.2.1 PFS Rate at Month 12 and Median PFS

The PFS response rate at month 12 and this measure derived as a time-to-event outcome, will be calculated in the same manner as the primary endpoint (see Section 8.1.1).

Scheduled disease assessment at cycle 19 day 1 will be used to determine PFS response rate at month 12.

8.2.2 Overall Survival (OS)

Overall survival (OS) will be defined as the time from first dose of study treatment until the date of death due to any cause. For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. OS will be calculated in days as OS = Date of death (or date of last known alive) - Date of first dose + 1.

The Kaplan-Meier method used in analyzing ~~PFS~~ will be used to summarize the median OS and the OS rate at Months 6 and 12.

8.2.3 Disease Control Rate (DCR)

Disease control rate (DCR) is defined as the proportion of patients with best overall response of SD longer than 6 weeks from first dosing, confirmed PR, or confirmed CR. The best overall response is defined in Section 8.2.4. DCR will be summarized at Month 6, Month 12, and EOS. Patients without an event will be considered as non-DCR. Associated 2-sided 95% CI will be presented by using the exact method (ie, Clopper-Pearson).

8.2.4 Overall Response Rate (ORR)

Overall response rate (ORR) is defined as the proportion of patients with best overall response of confirmed PR or confirmed CR. The best overall response is the best overall response recorded from the start of study treatment until the EOS considering any requirement for confirmation. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Patients who have obtained a response (PR or CR) will have a confirmatory scan at a minimum of 4 weeks following the initial scan. When stable disease (SD) is believed to be the best response, it must be a minimum of 6 weeks (42 days) ± 7 days for a minimum time on-study of 35 days from the first dose to documented evidence of SD. If the subject is on-study less than 35 days, any tumor assessment indicating stable disease before this time period will have a best response of NE unless PD is identified. Otherwise, the patient's best response depends on the subsequent assessment. The best overall response when confirmation of CR and PR is required is presented in **Table *10***. Patients without an event will be considered as non-ORR.

The ORR will be evaluated at Months 6 and 12, and at EOS.

Table 10 Best overall response when confirmation of CR and PR required

First Time Point Response**	Second Time Point Response	Confirmed Response (Best Response)*
PD	No further evaluation	PD
NE	PD	PD
CR	PD	SD or PD (1)
PR	PD	SD or PD (1)
SD	PD	SD or PD (1)
CR	CR	CR
CR	NE **	SD or NE (2)
PR	CR	PR
PR	PR	PR
PR	SD (3)**	SD
PR	NE **	SD or NE (2)
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE (2)
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE

Source: Independent Review Charter v1.0

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

* A Best response of SD can only be made after the subject is on-study for a minimum of six (6) weeks (42 days). If the subject is on-study less than six (6) weeks (42 days) ± seven (7) days, for a

minimum time on-study of thirty-five (35) days, any tumor assessment indicating stable disease before this time period will have a Best response of NE unless PD is identified.

** Subsequent documentation of CR may provide confirmation of a previously identified CR for subjects where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for subjects where the second integrated response was NE or SD. If the third time point response (TPR) confirms the CR (or PR) then the confirmed response will be CR (or PR). For this study, only 1 intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, 1 SD is allowed between PRs (eg, PR SD PR = PR). Note: in the following scenario, PR SD NE PR, the second PR is not a confirmed PR.

(1) Best response will be SD if the first TPR is after 35 days on-study. Otherwise, the best response will be PD.

(2) Best response will be SD if the first TPR is after 35 days on-study. Otherwise, the best response will be NE.

(3) TPR is SD if the increase from the first to the second assessment does not qualify for PD.

8.2.5 Local Radiologist's Assessment (PFS, ORR, and DCR)

Secondary sensitivity analysis will be performed to further evaluate the primary and secondary efficacy endpoints PFS, ORR, and DCR using the local radiologist's assessments. In addition, subgroup analysis will be applied PFS, ORR and DCR using the same method as described in Section 8.1.1, Section 8.2.3, Section 8.2.4, and Section 9.2.

8.2.6 Change in Tumor Size

A waterfall plot will be provided of change in tumor size (as of % of baseline) from baseline to Month 6 response for all patients for whom primary lesion data are available and will be displayed based on Safety population. Associated change from baseline summary table will be also provided.

8.2.7 Sensitivity Analysis

A separate sensitivity analysis will also be performed on all secondary efficacy tables as defined in Section 8.2 based on the PP population as well as by treatment cycle population.

9. Exploratory Analysis

Exploratory analyses will be performed on the Safety population.

9.1 Health-Related Quality of Life (HRQoL)

Quality of Life (QoL) will be assessed using the EORTC QLQ-C30 and QLQ-BIL21. Analyses will be based on the Safety population. Actual and change from Baseline for QLQ-C30 and QLQ-BIL21 total and subscale scores will be summarized at Baseline, Months 6 and 12 using descriptive statistics.

Each of the 30 scores of the EORTC QLQ-C30, as well as the 5 functional scales (physical, role, emotional, cognitive, social), and 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) will be summarized by visit. The analyses of the EORTC QLQ-C30 will be based on all treated patients who completed the Baseline assessment and had at least 1 post-Baseline assessment with the EORTC QLQ-C30. Actual values and changes from Baseline will be summarized for all patients overall.

The standard scoring procedures as suggested by the EORTC v3.0 will be followed. All of the scales and single item measures range in score from 0 to 100. A high scale score represents a high response level. For all scales, the raw score (RS) is the mean of the component items. The functional scales will be calculated as:

Score = (1- (RS-1)/range) x100, and

For symptom scales/items and global health status/QoL:

Score = ((RS-1) /range) x 100.

where range is the difference between the maximum possible value of RS and the minimum possible value.

Each of the 21 items of the EORTC QLQ-BIL21, as well as the 5 functional scales (eating, jaundice, tiredness, pain, anxiety) will be summarized by visit. The analyses of the EORTC QLQ-BIL21will be based on all treated patients who completed the Baseline assessment and had at least 1 post-Baseline assessment with the EORTC QLQ-BIL21. Actual values and changes from Baseline will be summarized for all patients overall.

The standard scoring procedures are in a similar fashion to the scoring for the EORTC QLQ-C30. All of the scales and single item measures range in score from 0 to 100. A high scale score represents a worse or more problems. For all scales, the raw score (RS) is the mean of the component items.

Score= (RS-1)/rangex100

Range is the difference between the maximum and minimum possible value of the raw score. All items are scored from 1 to 4, giving a range=3.

For each scale, the raw score will be calculated by the addition of item responses divided by the number of items. Then a linear transformation is used to standardize the raw score, so that scores range from 0 to 100. Please refer to Section 15.4 for the details of EORTC QLQ-BIL21 scoring.

The calculation of scores and methods to deal with missing data will be handled according to the respective questionnaires' standard scoring guidelines for both EORTC QLQ-C30 and QLQ-BIL21. If at least half of the items from the scale have been answered, all of the items that were completed are used and apply the standard equations given above: ignore any items with missing values when making the calculations. If less than half of the items from the scale have been answered, the scale score is set to missing. For single-item measures with missing response, the score is set to missing.

9.2 Subgroup Analysis

Subgroup analyses of PFS, OS, ORR, and DCR may be performed using both BICR and local radiologist's assessment, based on categorical subgroup group variables. Subgroup definition details are specified in Section 6.5.

9.3 Sensitivity Analysis

All efficacy analyses will be also conducted based on the PP population as well as by treatment cycle population.

10. Safety Analysis

Safety and tolerability will be evaluated through the collection and review of treatment-emergent adverse events (TEAEs), as graded by CTCAE v5.0, vital signs measurement, 12-lead electrocardiogram (ECG) findings, physical examination (PE) findings, and clinical laboratory parameters (chemistry, hematology, and urinalysis) including changes from Baseline and frequency of values meeting CTCAE Grades >1, CTCAE Grades 3/4 separately. In addition, shift table analyses will be applied to the laboratory data. All summaries will be performed using the Safety population.

All safety summaries will be descriptive; no statistical significance tests will be performed on the safety data.

Summaries will be prepared by study time point. Adverse events will also be prepared by PP population as well as by treatment cycle population. Adverse events will also be displayed by study drug cycle based on Safety population. All safety data will be listed by patient.

10.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related.

Treatment-emergent AEs (TEAEs) are defined as any AEs reported after the first dose of study drugs (XERMELO, cisplatin, and/or gemcitabine) and for 30 days following the last dose of study drugs.

Any treatment-emergent abnormal laboratory result should be and reported as an AE if it meets 1 or more of the following conditions:

- Fulfills any of the criteria for an SAE,
- Results in discontinuation of study treatment,
- Requires treatment, or
- Is considered by the Investigator to be clinically significant.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed based on Appendix 15.3.

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA**,** version 21.1 or later).

Patients with at least 1 TEAE will be summarized for the following:

- Overall summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT by decreasing frequency
- Summary of TEAEs by relationship to each study drug (XERMELO, cisplatin, and gemcitabine), SOC and PT
- Summary of TEAEs by relationship to each study drug (XERMELO, cisplatin, and gemcitabine) and PT
- Summary of TEAEs by maximum severity by SOC and PT
- Summary of TEAEs by study drug cycle
- Serious TEAEs by SOC and PT
- Death by SOC and PT
- TEAEs that leading to discontinuation from the study by SOC and PT
- TEAEs that leading to discontinuation from treatment by SOC and PT

- TEAEs that leading to treatment reduction by SOC and PT
- TEAEs that leading to XERMELO reduction by SOC and PT
- TEAEs that leading to XERMELO interruption by SOC and PT
- TEAEs with severity grade ≥ 1 by SOC and PT
- TEAEs with severity grade ≥ 2 by SOC and PT
- TEAEs with severity grade 3 and 4 by SOC and PT
- Adverse events of special interest (AESI) by SOC and PT

Summaries made by severity will select the event with the highest severity when multiple occurrences of the same event are reported for the same patient. In a similar manner, summaries prepared by drug relationship will select the event with the greatest degree of relationship when a patient reports multiple occurrences of the same event.

On-study deaths will be reported for deaths occurring during study participation and the 30 days after stopping study drug. Also, deaths occurring outside the 30-day window, but secondary to an AE reported within the 30-day Follow-up Period, will be reported as well.

All AE tables will be displayed based on safety population, PP population as well as by treatment cycle population. All AE tables by study drug cycle will also be displayed based on safety population.

10.1.1. Incidence of Adverse Events

An overall summary of TEAEs will be presented in a table and will include the number and incidence of patients with any TEAE, number of TEAEs, patients with serious TEAEs, patients with severe TEAE (≧ Grade 3), patients that discontinued from study due to TEAEs, TEAE leading to dose reduction, TEAE leading to discontinuation from treatment, and deaths. In addition, the table will include the number and percentage of patients in each category of severity (ie, Grade 1 to Grade 5) for all TEAEs and the number and percentage of patients in each category of relationship to each study drug (ie, “Related” and “Not Related”).

A related AE is an event where the investigator determined that the relationship to study drug was “Possibly Related”, “Probably Related” or “Definitely Related”. For summaries by relationship, adverse events with missing relationship are counted as “Possibly Related”. For summaries by CTCAE grade, adverse events with missing CTCAE grade are counted as CTCAE Grade 3 (Severe).

10.1.2. Treatment Emergent Adverse Events Summary by SOC and PT

Summaries of the total number of TEAEs and the number and percentage of patients with at least 1 TEAE will be provided. TEAEs will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported 1 or more events. Percentages will be calculated out of the number of patients in the Safety population.

The summary of TEAEs will be presented in descending order from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order.

Additional summary of TEAEs will be presented in descending order from the PT with the highest total incidence to the PT with the lowest total incidence.

All TEAEs will be presented in a listing.

10.1.3. Relationship of Adverse Events to Study Drug

A summary of total number of TEAEs and number and percentage of patients with at least 1 TEAE by relationship (ie, “Related” and “Not Related”) to each study drug, will be presented in a table by incidence of occurrence. If the relationship is missing, it will be considered as related in the summary table.

For each AE, the Investigator will assess the causal relationship between each of the study drugs and the AE using their clinical expertise and judgment. In the TEAE relationship table, if a patient reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. Percentages will be calculated out of the number of patients in the Safety population.

The TEAE data will be categorized and presented by SOC, PT, and relationship. Additional summary of TEAEs will be presented by PT and relationship.

10.1.4. Severity of Adverse Event

A summary of total number of TEAEs and number and percentage of patients with at least 1 TEAE by severity will be presented in a table.

The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are Grade 1 to Grade 5 (ie, “Mild”, “Moderate”, “Severe”, “Life-threatening”, and “Death”, respectively). If the severity is missing, it will be considered as severe in the summary table. In the TEAE severity table, if a patient

reported multiple occurrences of the same TEAE, only the most severe will be presented. Percentages will be calculated out of the number of patients in the Safety population.

The TEAE data will be categorized and presented by SOC, PT, and severity.

In addition, similar tables will be produced for TEAEs that have severity of Grade ≥ 1, Grade ≧ 2, and Grade 3/4 separately.

10.1.5. Adverse Events by Length of Exposure to Each Study Drug

TEAEs will be summarize separately by the total exposure cycles of XERMELO, cisplatin, and gemcitabine. TEAE will be categorized into 6 subgroups:

- exposure=0 or exposure ≦ C1;
- C1 < exposure ≦ C3;
- C3 < exposure ≦ C6;
- C6 < exposure ≦ C9;
- C9 < exposure ≦ C12;
- exposure > C12

Additional analysis by different exposure range (eg, every 4 cycles) might be performed upon reviewing the data.

10.1.6. Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, is a congenital anomaly/birth defect, requires in-patient hospitalization or prolongation, or results in significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Summaries of the total number of SAEs and the number and percentage of patients with at least 1 SAE will be provided. SAEs will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported 1 or more events. Percentages will be calculated out of the number of patients in the Safety population.

The summary of SAEs will be presented in descending order from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for

any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order.

All SAEs will be presented in a listing by patient using the Safety population. If there are no SAEs at the end of the study, the tables or listings will state that there are no SAEs in the study.

10.1.7. Adverse Events Leading to Study Discontinuation

A summary of the total number of TEAEs leading to study discontinuation and the number and percentage of patients with at least 1 TEAE that caused study discontinuation will be presented. TEAEs leading to study discontinuation will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported 1 or more events. Percentages will be calculated out of the number of patients in the Safety population within the subgroup category.

The summary of TEAEs that caused study discontinuation will also be presented in descending order of frequency from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order.

10.1.8. Adverse Events Leading to Treatment Discontinuation

A summary of total number of TEAEs leading to treatment discontinuation and number and percentage of patients with at least 1 TEAE that caused treatment discontinuation will be presented. TEAEs leading to treatment discontinuation will be defined as TEAEs leading to treatment discontinuation of either one of study drugs. TEAEs leading to treatment discontinuation will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported 1 or more events. Percentages will be calculated out of the number of patients in the Safety population within the subgroup category.

The summary of TEAEs that caused treatment discontinuation will also be presented in descending order of frequency from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order.

10.1.9. Adverse Events Leading to Dose Reduction

A summary of total number of TEAEs leading to dose reduction and number and percentage of patients with at least 1 TEAE that caused dose reduction will be presented. TEAEs leading to dose reduction will be defined as TEAEs leading to dose reduction of either one of study drugs. TEAEs leading to dose reduction will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported 1 or more events. Percentages will be calculated out of the number of patients in the Safety population within the subgroup category.

The summary of TEAEs that caused dose reduction will also be presented in descending order of frequency from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order.

10.1.10. Adverse Events Leading to XERMELO Reduction

A summary of total number of TEAEs leading to XERMELO reduction and number and percentage of patients with at least 1 TEAE that caused XERMELO reduction will be presented. TEAEs leading to XERMELO reduction will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported 1 or more events. Percentages will be calculated out of the number of patients in the Safety population within the subgroup category.

The summary of TEAEs that caused XERMELO reduction will also be presented in descending order of frequency from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order.

10.1.11. Adverse Events Leading to XERMELO Interruption

A summary of total number of TEAEs leading to XERMELO interruption and number and percentage of patients with at least 1 TEAE that caused XERMELO interruption will be presented. TEAEs leading to XERMELO interruption will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported 1 or more events. Percentages will be calculated out of the number of patients in the Safety population within the subgroup category.

The summary of TEAEs that caused XERMELO interruption will also be presented in descending order of frequency from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any 2 or more SOCs is equal, the

SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in descending order.

10.1.12. Adverse Events of Special Interest

Based on the mechanism of action of telotristat etiprate, and observations in the clinical studies, monitoring of depression-related AEs will be the responsibility of the Sponsor. Refer to Section 15.2 for a list of preferred terms that will be considered as a depression-related AESI if deemed clinically significant by the Investigator.

Depression-related adverse events will be presented in frequency tables for number and percentage of patients with any depression-related adverse events and by SOC and PT. Similarly, Suicide/Self injury-related adverse events and liver-related AEs will be presented in frequency tables by SOC and PT separately. In addition, hepatic enzyme increase safety analysis will be addressed and presented in part by summarizing the number and percentage of subjects who had AEs that relate to liver function. A list of preferred terms that correspond to depression, suicide/self-injury and hepatic enzyme increase related adverse events will be identified using a subset of PTs selected from narrow scope PTs in the SMQ.

10.1.13. Deaths

On-study deaths will be reported for deaths occurring during study participation and the 30 days after stopping study drug. Also, deaths occurring outside the 30-day window, but secondary to an AE reported within the 30-day Follow-up Period, will be reported as well.

Deaths will be presented in frequency tables for number and percentage of patients with any death and by SOC and PT. Listings will be provided for deaths.

10.2. Clinical Laboratory Evaluations

Clinical laboratory assessments will include, at a minimum, blood chemistry (complete metabolic profile [CMP], liver function tests [alkaline phosphatase (ALKP), ALT, AST, total bilirubin], lipid panel [high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglycerides], coagulation parameters [PT, INR]), hematology (complete blood count [CBC] with differential, and platelet counts), and urinalysis.

Out of range values should be assessed by the Investigator for clinical significance relevant to the patient population. For this protocol, assessments will be defined as not clinically significant (NCS) or clinically significant (CS).

Summary tabulations (ie, n, mean, SD, median, minimum, and maximum) for the observed values and changes from Baseline will be presented for clinical laboratory evaluations with numeric values for patients in the Safety population. Observed results at each visit and changes from Baseline for each scheduled post-Baseline visit will be presented.

All relevant clinical laboratory tests will be classified as Low, Normal, and High according to the normal ranges. This categorical data will be summarized in shift tables based on normal range comparing the results at worst post-Baseline value (minimum or maximum value of any post-Baseline visit) with those at the Baseline visit.

Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (ie, no visit windows will be applied). Unscheduled data will be included in the shift table summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment.

All individual laboratory values will be listed by visit.

10.2.1. Serum Albumin

Actual, and change from Baseline in serum albumin results will be summarized in a separate table by Baseline, Month 6, Month 12, and EOS using descriptive statistics.

10.2.2. Pregnancy Test

Additional assessments such as serum and urine pregnancy tests will be performed on females of childbearing potential only. The urine pregnancy test will be performed by the site staff with the provided laboratory kit.

Pregnancy test details will be listed.

10.3. Vital Sign Measurements

Measurement of vital signs will include assessment of blood pressure, respiratory rate, pulse rate, temperature, and body weight.

Summary tabulations (ie, n, mean, SD, median, minimum, and maximum) for the observed values and changes from Baseline will be presented for vital sign data for patients in the Safety population. Changes from Baseline to each scheduled post-Baseline time point and

visit will be presented. Baseline is defined as last measurement before first dose of study. Figure for mean weight change over time will be provided.

For weight, the proportions with stable weight, weight gain, weight loss will also be summarized. Stable weight is defined as a change from baseline to week 24 of less than 3%. Weight gain is an increase of at least 3%, and weight loss is a reduction of at least 3%.

All vital sign data by patient will be presented in a listing.

10.4. Physical Examination

Physical examination findings will be listed.

10.5. Electrocardiogram

Summary of actual value and change from Baseline will be presented in a summary table for patients in the Safety population. Overall interpretation is assessed as normal, abnormal, not clinically significant, clinically significant. A shift table from Baseline to current visit will be presented for the overall interpretation. The categories of QTcB and QTcF (≤450 msec, >450-480 msec, >480-500 msec, >500 msec) and the categories of change from Baseline for QTcB and QTcF (≥30 msec and ≥60 msec) will be summarized by visit.

ECG data for all patients will be presented in a listing.

10.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

Actual and change from Baseline in ECOG will be summarized by time point using descriptive statistics.

All measurements will be displayed in a data listing.

10.7. Depression Detection

Patients will be evaluated for depression prior to initiating treatment on Day 1, then periodically throughout the remaining duration of the study as outlined in Section 15.1.

Frequency tables on responses to depression detection questions per visit will be presented. The responses of patients will also be listed.

10.8. Other Safety Data

Observed values at Baseline for serotonin [5-HT] and tryptophan hydroxylase-1 [TPH-1] will be summarized using descriptive statistics to assess the effect of study treatment based on characterization of tumor tissue by immunohistochemical (IHC) staining.

Immunohistochemical (IHC) staining details will be listed.

11. Pharmacokinetics

11.1 Pharmacokinetic Sample Concentrations

Blood samples for plasma PK analysis of XERMELO and the active metabolite, LP-778902 will be collected at the following time points:

Predose, 1, 2, 4, and 6 hours on C1D1 and C1D8.
Predose on C2D1, C3D1, C4D1, C5D1, C6D1, C7D1, C8D1, C9D1, and EOT

Plasma concentration and time deviation data will be presented in data listings by cycle, day, and nominal time point for the Safety population. Plasma concentration data will be summarized by cycle, day, and nominal time point for the PK population using descriptive statistics: number of patients with non-missing data (n), mean, SD, coefficient variance (CV), median, minimum, and maximum. All plasma concentration values below the limit of quantification (BLQ) will be set to zero when calculating summary statistics.

Mean plasma concentration versus nominal time profiles on C1D1 and C1D8 will be presented on both linear and semilogarithmic scales for the PK population. Individual plasma concentration versus actual time profiles on C1D1 and C1D8 will be presented on both linear and semilogarithmic scales by dose for the Safety population. In addition, mean and individual trough concentration on Day 1 of each cycle versus time profiles will be presented on linear scale.

11.2 Pharmacokinetic Parameters

Where possible, the individual plasma concentration versus actual time data for XERMELO and LP-778902 will be used to derive the following PK parameters, by noncompartmental methods using Phoenix® WinNonlin® Version 8.0 or higher (Certara USA, Inc., Princeton, NJ).

PK Parameter	Definition
C_{max}	observed maximum plasma concentration

C_{trough}	trough plasma concentration (predose concentration)
t_{max}	time of maximum observed plasma concentration
$AUC_{(0-6)}$	area under the plasma concentration-time curve from time zero to 6 hours after dose administration.
$AUC_{(0-last)}$	area under the plasma concentration-time curve from time zero to time of last measurable concentration
Kel	apparent first-order terminal rate constant
t½	apparent terminal elimination half-life

For the calculation of PK parameters, all plasma concentrations that are BLQ prior to the first measurable concentration will be set to zero and treated as missing thereafter.

C_{trough} values will also be listed and summarized, and mean trough values will be plotted.

Individual PK parameters will be presented in data listings for the PK population. The PK parameters will be summarized for the PK population using the following descriptive statistics: n, mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. For t_{max}, only n, median, minimum, and maximum will be reported.

12. Pharmacodynamics

Pharmacodynamic assessments include the determination of [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] will be summarized at Month 6, Month 12, and EOS using descriptive statistics and 1-sample t-tests may be performed to test for significance using a 5% level of significance.

Pharmacodynamics data for all patients will be presented in a listing.

13. Interim Analysis

Stage 1 analysis

Stage 1 enrollment will include a Safety Run-in cohort. Safety and tolerability data of the combination treatment from the first 6 patients who complete at least 21 days of safety follow-up after the first dose of combination treatment will be evaluated. During this review, Stage 1 enrollment will continue. It is anticipated that a total of 20 patients will participate in Stage 1. If there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and if of 12 (60%) or more of the 20 patients enrolled are deemed PFS responders in the Safety population, enrollment will continue to

Stage 2. In addition, selected efficacy will be assessed in the per-protocol population and by treatment cycle.

Stage (1 + 2) analysis and Interim Analyses:

Formal statistical interim analyses will be performed during this study as follows:

- Interim analysis 1 : Conducted in Patients included in the Stage 1 analysis (first 20 patients enrolled) and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data.
- Interim analysis 2 added to (Stage 1+2) 6 month analysis : Conducted after all 53 Patients (Stage 1 + Stage 2) complete the Month 6 visit, and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle population.
- Interim Analysis 3 added to (Stage 1+2) 12 month analysis: Conducted after all 53 Patients (Stage 1 + Stage 2) complete the Month 12 visit, and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle population.

14. References

1. TerSera LX1606.1-207-BTC Protocol: A Phase 2, Multicenter, Open-label, Safety and Efficacy Study of XERMELO® (Telotristat Ethyl) plus First-line Chemotherapy in Patients with Locally Advanced, Unresectable, Recurrent **or** Metastatic Biliary Tract Cancer (BTC)
2. Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials.* 1989 Mar;10(1):1-10.
3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) *Eur J Cancer*. 2009;45:228–247.
4. National Comprehensive Cancer Network®. NCCN Guidelines® v 1.2018 Neuroendocrine and Adrenal Tumors. March 29, 2018.
5. Sarrouilhe D, Clarhaut J, Defamie N, Mesnil M. Serotonin and cancer: what is the link? *Curr Mol Med*. 2015;15(1):62-77.
6. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual (3rd Edition).*Brussels 2001.

15. Appendices

15.1. Schedule of Study Procedures

Schedule of Events:

Procedure	Treatment Period[2,3,4] (1 cycle = 21 days, with Cis/Gem treatment on D1 & D8 and XERMELO treatment daily)																				
	Screening[1] (Up to 21 days)	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	C13 D1	C14 D1	C15 D1	C16 D1	C17 D1	C18 D1	C19 D1	EOT [5,6]
Window (days)	NA	NA	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4
Assess IE criteria	X	X																			
Medical history and demographics	X																				
Full physical exam[7]	X	X																			X
Symptom-oriented, brief physical exam[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																				
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[8]	X																				
Urine pregnancy test[8]		X																			X
Hematology[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Blood chemistry[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Serum CA 19-9[9,11]		X			X			X			X			X			X			X	X[10]
Serum CEA[9]		X			X			X			X			X			X			X	X[10]
Plasma 5-HIAA[9]		X			X			X			X			X			X			X	X[10]
PK trough sample[9,12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]
Urinalysis	X	X			X			X			X			X			X			X	X[10]
Tumor Assessment[13] (CT or MRI)	X[1]	X[1]			X			X			X			X			X			X	X[10]
ECG	X	X			X			X			X			X			X			X	X[10]

Procedure	Treatment Period[2,3,4] (1 cycle = 21 days, with Cis/Gem treatment on D1 & D8 and XERMELO treatment daily)																			
	Screening[1] (Up to 21 days)	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	C13 D1	C14 D1	C15 D1	C16 D1	C17 D1	C18 D1	C19 D1	EOT [5,6]
Window (days)	NA	NA	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4
ECOG Performance	X	X			X			X			X			X			X			X	X
Depression detection (ePRO)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EORTC QLQ-30 and QLQ-BIL21 (ePRO)		X																			X
Record concomitant medications[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs and AESIs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Xermelo[4,15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[16]
Cis/Gem Infusion[17]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Intensive PK substudy[18]		X			X			X			X			X			X			X	
Tumor characterization substudy[19]	X																				

Procedure	Follow-up Period[20,21]															
	Post-treatment Follow-up								Survival Follow-up							
	3 Month	6 Month	9 Month	12 Month	15 Month	18 Month	21 Month	24 Month / EOS[6]	3 Month	6 Month	9 Month	12 Month	15 Month	18 Month	21 Month	24 Month
Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Phone patient[22]									X	X	X	X	X	X	X	X
Full physical exam[7]								X								
Symptom-oriented brief physical exam[7]	X	X	X	X	X	X	X									
Weight								X								
Vital signs	X	X	X	X	X	X	X	X								
Urine pregnancy test[8]								X								
Hematology[9]	X	X	X	X	X	X	X	X[10]								
Blood chemistry[9]	X	X	X	X	X	X	X	X[10]								
Serum CA 19-9[9,11]	X	X	X	X	X	X	X	X[10]								
Serum CEA[9]	X	X	X	X	X	X	X	X[10]								
Plasma 5-HIAA[9]	X	X	X	X	X	X	X	X[10]								
PK trough sample[9,12]	X	X	X	X	X	X	X	X[10]								
Urinalysis								X[10]								
Tumor Assessment[13] (CT or MRI)	X[23]	X[23]	X	X	X	X	X[23]	X[10,23]								
ECG								X[10]								
ECOG Performance	X	X	X	X	X	X	X	X								
Depression detection (ePRO)								X								
EORTC QLQ-30 and QLQ-BIL21 (ePRO)		X						X								
Record concomitant medications[18]	X	X	X	X	X	X	X	X								
Record SAEs	X	X	X	X	X	X	X	X								
Record AEs and AESIs	X	X	X	X	X	X	X	X								
Dispense Xermelo[4,15]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]									

AE = adverse event; AESI = adverse event of special interest; CT = computed tomography; Cis = cisplatin; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; Gem = gemcitabine; IE = inclusion/exclusion; MRI = magnetic resonance imaging; SAE = serious adverse event; PK = pharmacokinetic

Schedule of Events Footnotes

1. The Screening Visit allows for up to 21 days prior to C1D1 if needed; however, if radiological assessments have been completed within 6 weeks prior to Day 1, they are not required to be repeated at Day 1.
2. All assessments, including laboratory assessments, ECGs and questionnaires should be performed prior to initiating treatment regimen.
3. Treatment visit dates will be scheduled based on the date of enrollment.
4. All cycles are 21 days, with Cis/Gem treatment on D1 and D8 and XERMELO treatment daily. Patients are not required to complete a specific amount of cycles, patients may continue combination treatment for as many cycles possible until PD, unacceptable toxicity, or patient withdraws from treatment.
5. EOT procedures should be completed once the patient has confirmed PD, unacceptable toxicity, or withdraws from combination treatment. The patient will then begin the Post-treatment Follow-up Period (PTFP) where patients return to the site every 3 months to complete the required assessments until a new tumor directed therapy begins, the patient declines further treatment after progression, or withdraws from any further study visits. At that time, the EOS procedures should be completed and the patient should enter the Survival Follow-up Period (SFP) until the patient has completed a full 24 months of combination Post-treatment/Survival Follow-up. During SFP patients are to be contacted by phone every 3 months to obtain survival status; see Section 5.1.2.2 of protocol for details.
6. Procedures should not be repeated if end of treatment (EOT)/end of study (EOS) occurs during scheduled study visit; however, all EOT/EOS assessments should be completed; with those required by the scheduled visit to be recorded on the scheduled visit eCRF and additional assessments required by EOT/EOS recorded in the EOS eCRF.
7. A complete physical examination will include, at minimum, a review of the patient's general appearance, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, back, extremities, skin and general neurological system. A symptom-related brief physical exam will only occur if the patient is experiencing symptoms or AEs. If a symptom-related brief physical exam is required, it should include a review of all body systems that relate to the symptoms and/or AE the patient is experiencing.
8. Females of childbearing potential only
9. Day 8 labs are optional (at the discretion of the Investigator) and will be analyzed by the local lab.
10. EOT assessments are not required if the last assessment occurred <3weeks prior; EOS assessments are not required if last assessment occurred ≤8weeks prior.
11. Patients should avoid multivitamins or dietary supplements containing biotin (vitamin B7) for 12 hours prior to sample collection.
12. PK trough samples are required to be drawn for ALL patients. Patients should be in a fasted state and should not have dosed prior to blood draw.
13. Tumor assessments are not required if progressive disease has been confirmed by CT/MRI at previous visit.
14. Prior medications taken within 30 days of screening will be recorded within the patient's medical history. Any medications that are ongoing at the time of screening should be recorded within the patient's concomitant medication page.
15. Xermelo will be dispensed on D1 of each cycle. The patient should be reminded to bring their bottles back on D8 of each cycle in order for dosing of Xermelo to be given with the chemotherapy infusion.
16. Xermelo can continue to be dispensed during the Post-treatment Follow-up Period, at the discretion of the Investigator, until the patient begins new tumor-directed therapy, declines further treatment after progression, or withdraws from any further study visits.
17. Cis/Gem are not being provided by TerSera. If cisplatin is stopped, gemcitabine may be continued alone at the Investigator's discretion.
18. Intensive PK is an optional substudy. These samples are only required for those patients who have consented to participate in this substudy and will be drawn on Day 1 and Day 8 of each cycle where collected; refer to Intensive PK Substudy Schedule of protocol for additional details.
19. Archived tissue samples can be submitted at any time during the Treatment Period. Fresh biopsies will not be collected.
20. Total duration of the 2 combined Follow-up Periods should be no more than 24 Months.
21. Follow-up visits dates should be scheduled based on the EOT date.

22. Phone call to patient or caregiver, where appropriate, to obtain survival status.
23. 23. Patients who enter PTFP and imaging assessments are not required, or who enter SFP without entering or completing PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the 6-month timepoint. Reconsenting the patient may be required if previously prematurely discontinued or withdrew consent from the Treatment Period of the study.

Intensive PK Substudy Schedule

Schedule of Intensive PK Assessments[1]								
	Predose	Morning Dose[2]	1 hr	2 hr	3 hr	4 hr	6 hr	Midday Dose
Intensive PK Assessments	X		X[4]	X[4]		X[4]	X[4]	
Time of Day (Example)	Predose[3]	8:00	9:00	10:00	11:00	12:00	14:00	14:01

[1]Patients who have consented to the intensive PK substudy should have PK samples collected at all time points shown above on Day 1 and Day 8 of all required cycles; see Schedule of Events.
[2]With food
[3]Fasted
[4]Samples should be collected within 15 minutes of scheduled collection time

15.2. Terms Considered Depression-related AESI, if Clinically Significant

Please see below narrow PTs based on the Depression (excl suicide and self injury) SMQ and Suicide/self-injury (SMQ). MedDRA v. 22.1. The PTs might be updated if later MedDRA version is used for the study.

Depression

- Adjustment disorder with depressed mood
- Adjustment disorder with mixed anxiety and depressed mood
- Agitated depression
- Anhedonia
- Antidepressant therapy
- Childhood depression
- Decreased interest
- Depressed mood
- Depression
- Depression postoperative
- Depressive symptom
- Dysphoria
- Electroconvulsive therapy
- Feeling guilty
- Feeling of despair
- Feelings of worthlessness
- Helplessness
- Major depression
- Menopausal depression
- Mixed anxiety and depressive disorder
- Perinatal depression
- Persistent depressive disorder

Assisted suicide

- Columbia suicide severity rating scale abnormal
- Completed suicide
- Depression suicidal
- Intentional overdose
- Intentional self-injury
- Poisoning deliberate
- Self-injurious ideation
- Suicidal behaviour
- Suicidal ideation
- Suicide attempt
- Suicide threat
- Suspected suicide
- Suspected suicide attempt

15.3. Imputation

Adverse Event and Concomitant Medications

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month, and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date
- If onset date is completely missing and the end date (after any imputation) is on or after the first dose of study drug, then onset date is set to date of first dose.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY

Medical History and Disease Diagnosis

Missing onset dates/diagnosis date (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug - 1. If the month and year are the same as the first dose of study drug month, and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is

on or after the first dose of study drug, then assume the date of the first dose of study drug - 1. If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date

- If onset date is completely missing and the end date (after any imputation) is on or after the first dose of study drug, then onset date is set to date of first dose.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY
- If the end date after any imputation is on or after the first dose of study drug, then set to date of first dose - 1.

CCI

CCI

CCI

CCI

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15.5. Visit Cycles and Analysis Timepoints

Table 11: Visit Cycles and Analysis Timepoints

Cycle (Number) Day 1	Number of Days (± window days*)	Analysis Timepoint
Cycle 1 Day 1	21 days (± 0)	Baseline
Cycle 2 Day 1	42 days (± 4)	
Cycle 3 Day 1	63 days (± 4)	
Cycle 4 Day 1	84 days (± 4)	
Cycle 5 Day 1	105 days (± 4)	
Cycle 6 Day 1	126 days (± 4)	
Cycle 7 Day 1	147 days (± 4)	
Cycle 8 Day 1	168 days (± 4)	
Cycle 9 Day 1	189 days (± 4)	
Cycle 10 Day 1	210 days (± 4)	Month 6
Cycle 11 Day 1	231 days (± 4)	
Cycle 12 Day 1	252 days (± 4)	
Cycle 13 Day 1	273 days (± 4)	
Cycle 14 Day 1	294 days (± 4)	
Cycle 15 Day 1	315 days (± 4)	
Cycle 16 Day 1	336 days (± 4)	

Cycle 17 Day 1	357 days (± 4)	
Cycle 18 Day 1	378 days (± 4)	
Cycle 19 Day 1	399 days (± 4)	Month 12
End of Treatment	(± 4)	

* Nominal visit window pre-specified in protocol and the visit windows are not applicable to analysis windows.

15.6. Detailed Summary of SAP Changes

Section	Former Text	New Text (in Bold)	Rationale
Cover Page	Lexicon Pharmaceuticals, Inc.	TerSera Therapeutics LLC	Sponsor changed
Cover Page	Prepared by: PPD 929 North Front Street Wilmington, NC 28401	Prepared by: PPD 929 North Front Street Wilmington, NC 28401 **and** **TerSera Therapeutics LLC** **520 Lake Cook Road, Suite 500** **Deerfield, IL 60015**	Sponsor changed
List of Abbreviations, C1D1	Cycle 1, Day 1; Baseline	Cycle 1, Day 1; Baseline **(Baseline value is defined as the last non-missing data on or before the first dose of the study drug, unless otherwise specified)**	Clarificaiton requested by TerSera
List of Abbreviations, C10D1		Cycle 10 Day 1 is intended as Month 6	New abbreviation
List of Abbreviations, C19D1		Cycle 19 Day 1 is intended as Month 12	New abbreviation
List of Abbreviations, DCR	disease control rate defined as CR+PD+SD	disease control rate defined as CR+**PR**+SD	Fixed the error
List of Abbreviations, LFT		liver function test	New abbreviation
List of Abbreviations, PTFP	post-treatment follow-up	post-treatment follow-up **period**	Fixed the error
List of Abbreviations, SFP		survival follow-up period	New abbreviation
Section 1, Introduction	This study is intended to assess the effect of XERMELO in combination with 1L chemotherapy on progression-free survival (PFS) in patients with locally advanced,	This study is intended to assess the **safety and the** effect of XERMELO in combination with 1L chemotherapy on progression-free survival (PFS) in patients with locally advanced, unresectable,	Updated based on protocol amendment 3, Section 4.1 Primary Objective

	unresectable, recurrent or metastatic BTC who are naïve to tumor-directed therapy in the locally advanced or metastatic setting and for which treatment with 1L therapy is planned.	recurrent or metastatic BTC who are naïve to tumor-directed therapy in the locally advanced or metastatic setting and for which treatment with 1L therapy is planned.	
Section 2.1, Primary Objective	The primary objective of the study is to assess the safety and efficacy (PFS rate at Month 6) ~~of XERMELO in combination with cisplatin (cis) plus gemcitabine (gem).~~	The primary objective of the study is to assess the safety and efficacy (PFS rate at Month 6) **in the Safety population receiving the combination of XERMELO plus 1L treatment with cis/gem combination chemotherapy. Efficacy (PFS rate at Month 6) will also be evaluated in the Per Protocol Population (PP) and by treatment cycle.**	Updated based on protocol amendment 3, Section 4.1 Primary Objective
Section 2.2, Secondary Objective	To assess the effect of study treatment on the following: ... • Disease control rate (DCR); defined as complete response (CR) + partial response (PR) + stable disease (SD) at Months 6 ~~and~~ 12 and End-of-Study (EOS) • Objective response rate (ORR) defined as CR + PR at Months 6 ~~and~~ 12 and EOS ... • Change from Baseline in [redacted] at Months 6 ~~and~~ 12 and EOS	To assess the effect of study treatment on the following: ... • Disease control rate (DCR); defined as complete response (CR) + partial response (PR) + stable disease (SD) at Months 6**,** 12 and End-of-Study (EOS) • Objective response rate (ORR) defined as CR + PR at Months 6**,** 12 and EOS ... • Change from Baseline in [redacted] at Months 6**,** 12 and EOS • Change from Baseline in body weight at Months 6**,** 12 and EOS • Change from Baseline in serum albumin at Months 6**,** 12 and EOS	Grammar updated

	• Change from Baseline in body weight at Months 6 ~~and~~ 12 and EOS • Change from Baseline in serum albumin at Months, 6 ~~and~~ 12 and EOS Note: Unless otherwise indicated, all radiologic endpoints will be based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as determined by blinded independent central review (BICR~~) and compared to published historical data of cisplatin/gemcitabine (cis/gem) alone.~~).	Note: Unless otherwise indicated, all radiologic endpoints will be based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as determined by blinded independent central review (BICR**).**	
Section 2.3, Exploratory Objective	To assess the effect of study treatment on the following: • Changes in health-related quality of life (HRQoL) as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Cholangiocarcinoma and Gallbladder Cancer (QLQ-BIL21) items ~~at~~ Baseline, Months 6 and 12 • Change from Baseline in [redacted]	To assess the effect of study treatment on the following: • Changes in health-related quality of life (HRQoL) as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Cholangiocarcinoma and Gallbladder Cancer (QLQ-BIL21) items **from** Baseline, **at** Months 6 and 12 • Change from Baseline in [redacted] **at Months 6, 12 and EOS** Added: • **Subgroup analyses in:** **o Patients with changes in liver function tests**	Updated based on protocol amendment 3, Section 4.3 Exploratory Objectives

		o Patients with Biliary stents **o Location of disease (intrahepatic, extrahepatic , or gallbladder)** **o prior therapy** **o ECOG performance status** **• Efficacy analysis by treatment cycle population.**	
Section 3.1, Overall Study Design and Plan	The study involves: Screening, Treatment Period with Stages 1 and 2, Post-treatment Follow-up (PTFP), and Survival Follow-up.	The study involves: Screening, Treatment Period with Stages 1 and 2, Post-treatment Follow-up **Period** (PTFP), and Survival Follow-up. Added: **If there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug, and if 12 or more (≥60%) of the 20 patients enrolled who are deemed responder, enrollment will continue to Stage 2.**	Updated based on protocol amendment 3, Synopsis, Methodology
Section 3.1, Overall Study Design and Plan	Stage 2 may initiate ~~and continue~~ enrollment ~~upon completion of the~~ Stage 1 enrollment. ~~If fewer than 12 PFS responders are observed at Stage 1, patient accrual will be halted, and~~ the study ~~regimen declared "inactive". In the case that 12 or more PFS responders are observed at Stage 1, an~~ additional 33 patients ~~will be enrolled~~ for Stage 2. Study ~~duration and~~ assessments in	Stage 2 may initiate enrollment **once** Stage 1 enrollment **has been completed, in the absence of significant or unresolved Grade 3 or higher toxicities considered related to** the study **drugs**. **Approximately** 33 additional patients **are anticipated to participate in** Stage 2. Study assessments in this stage will be identical to Stage 1. From a total of 53 accrued patients from Stage 1 + Stage 2, if 34 **(>60%)** or more	Updated based on protocol amendment 3, Section 5.1.2.1, Treatment Period and Section 5.1.2.2, Follow-up Periods

	this stage will be identical to Stage 1. From a total of 53 accrued patients from Stage 1 + Stage 2, if 34 or more ~~positive~~ responses are observed (ie, patients are alive and progression-free at Month 6), the study will be ~~considered~~ successful. All patients are expected to be followed for a total duration of 24 months after the Treatment Period, unless they voluntarily withdraw consent from future study visits or assessments.	responses are observed (**i.e.,** patients are alive and progression-free at Month 6) **in the Safety population,** the study will be **declared** successful. **Efficacy will also be assessed in the PP population and by treatment cycle population.** All patients are expected to be followed for a total duration of 24 months after the Treatment Period, unless they **prematurely discontinue or** voluntarily withdraw consent from future study visits or assessments. .... Added: **Note: Patients who enter PTFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint. This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.** **Note: Patients who enter SFP without entering or completing PTFP and who entered SFP prior to having their 6-month imaging assessment in the Treatment Period, will be asked to consent to provide their local scans and/or local scan report closest to the Treatment Period 6-month timepoint.**	

		This includes the possible reconsenting of patients previously prematurely discontinued or withdrew consent from the Treatment Period of the study.	
Section 3.2.1, Primary Endpoint	3.2.1 Primary Endpoint The primary efficacy endpoint is PFS rate at Month 6, where patient progression is defined as the time from ~~Baseline~~ until the first determination of PD by central radiologic reading using RECIST v1.1 (Eisenhauer, 2009) or death from any cause.	3.2.1 Primary Endpoint **The primary endpoint of the study is to assess the safety, tolerability and efficacy of XERMELO in combination with cisplatin (cis) plus gemcitabine (gem).** **3.2.1.1 Primary Efficacy Endpoint** The primary efficacy endpoint is PFS rate at Month 6, where patient **disease** progression is defined as the time from **first dose date** until the first determination of PD by central radiologic reading using RECIST v1.1 (Eisenhauer, 2009) or death from any cause.	Updated based on protocol amendment 3, Section 4.1 Primary Objective
Section 3.2.2, Secondary Endpoints	• PFS rate at Month 12 and median PFS • DCR defined as CR + PR + SD at Months 6 ~~and~~ 12 and EOS • ORR defined as CR + PR at Months 6 ~~and~~ 12 and EOS • Local radiologist's assessment of PFS, ORR and DCR • Change from Baseline in [redacted] CCI [redacted] at Months 6 ~~and~~ 12 and EOS • Change from Baseline in body weight at Months 6 ~~and~~ 12 and EOS	• PFS rate at Month 12 and median PFS **at Month 12** • DCR defined as CR + PR + SD at Months 6**,** 12 and EOS • ORR defined as CR + PR at Months 6**,** 12 and EOS • Local radiologist's assessment of PFS, ORR and DCR • Change from Baseline in [redacted] CCI [redacted] at Months 6**,** 12 and EOS • Change from Baseline in body weight at Months 6**,** 12 and EOS	Updated based on protocol amendment 3, Section 4.2, Secondary Objective

	• Change from Baseline in serum albumin at Months 6 ~~and~~ 12 and EOS	• Change from Baseline in serum albumin at Months 6**,** 12 and EOS	
Section 3.2.3, Exploratory Endpoints	• Changes in HRQoL as measured by EORTC QLQ-C30 and QLQ-BIL21 items at Baseline, Months 6 and 12 • [redacted]	Added: **Note: Unless otherwise indicated, all radiologic endpoints will be based on RECIST v1.1 as determined by BICR.** … • Changes in HRQoL as measured by EORTC QLQ-C30 and QLQ-BIL21 items at Baseline, Months 6 and 12 • Change from Baseline in CEA fragment **at month 6, 12 and EOS** ... Added: • **Subgroup analyses in:** **o Patients with changes in liver function tests** **o Patients with Biliary stents** **o Location of disease (Histology: intrahepatic, extrahepatic , or gallbladder)** **o prior therapy** **o ECOG performance status** • **Efficacy analysis by treatment cycle (such as in patients who completed [redacted] with combination treatment.**	Updated based on protocol amendment 3, Section 4.3 Exploratory Objectives
Section 3.2.6, Safety Endpoints	• Incidence of TEAEs, TEAEs by severity, TEAEs by relationship to each of the study drugs, TEAEs by study drugs exposure time, TEAEs leading to	• Incidence of TEAEs, TEAEs by severity, TEAEs by relationship to each of the study drugs, TEAEs by study drugs exposure time, TEAEs leading to discontinuation from the study, **TEAE leading to dose reduction, TEAE leading**	Added per TerSera's request

	discontinuation from the study, SAEs, and deaths • Actual and change from Baseline in clinical laboratory results including frequency of values meeting NCI CTCAE Grades >1	**to XERMELO reduction, TEAE leading to XERMELO interruption, TEAE leading to discontinuation from treatment,** SAEs, and deaths • Actual and change from Baseline in clinical laboratory results including frequency of values meeting NCI CTCAE Grades >1**, laboratory data toxicities as defined by NCI CTCAE v5.0**	
Section 3.3, Treatments	… Patients may continue to receive combination treatment as described above for as many cycles as possible until PD as determined by local review, unacceptable toxicity, or the patient withdraws from treatment.	Added: **Note: Patients may continue to receive treatment for as many cycles possible, until progressive disease (PD) (up to 19 cycles during the Treatment Period), and during the Post Treatment Follow-up Period (up to an additional 24 months) at the discretion of the Investigator.** ... Patients may continue to receive combination treatment as described above for as many cycles as possible until PD as determined by local review, unacceptable toxicity, **prematurely discontinue,** or the patient withdraws from treatment.	Updated based on protocol amendment 3, Section 5.1.2.1, Treatment Period
Section 3.4, Dose Adjustment/Modifications	• Discontinuation: ~~premature~~ withdrawal from 1 or both treatments of the assigned combination treatment (XERMELO and/or 1L) defined as a dose interruption lasting for >3 weeks (XERMELO) or a missed cycle (cis/gem). Note, however, that discontinuation of cisplatin, but	• Discontinuation: **prematurely discontinue or prematurely** withdrawal from 1 or both treatments of the assigned combination treatment (XERMELO and/or 1L) defined as a dose interruption lasting for >3 weeks (XERMELO) or a missed cycle (cis/gem). Note, however, that discontinuation of cisplatin, but continuation of treatment with gemcitabine	Updated based on protocol amendment 3, Section 5.1.2.2, Follow-up Periods

	continuation of treatment with gemcitabine alone, will not be classified as discontinuation.	alone, will not be classified as discontinuation.	
Section 4, General Statistical Considerations	... Demographic data, Baseline disease characteristics, prior and concomitant medications, treatment compliance, treatment exposure, AE, laboratory tests, vital signs, PE findings, 12-lead ECG findings, and final disposition will be summarized descriptively. No statistical tests will be performed. Analyses will be based on the Safety population.	Added: **For the purpose of statistical analyses, Cycle 10 Day 1 is intended as Month 6, and Cycle 19 Day 1 is intended as Month 12.** … Demographic data, Baseline disease characteristics, prior and concomitant medications, treatment compliance, treatment exposure, AE, laboratory tests, vital signs, PE findings, 12-lead ECG findings, and final disposition will be summarized descriptively. **In addition, shift table analyses will be applied to the laboratory data.** No statistical tests will be performed. Analyses will be based on the Safety population.	Updated based on protocol amendment 3, Synopsis, Methodology and Section 10.4.2, Safety Analyses
Section 4.1, Sample Size	The sample size was computed by satisfying design assumptions for the primary endpoint of the study; which is to assess the PFS responder rate at Month 6.	The sample size was computed by satisfying design assumptions for the primary **efficacy** endpoint of the study; which is to assess the PFS responder rate at Month 6. … Added: **In the Stage 1 Safety population, if there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and if 12 (60%) or more of the 20 patients enrolled who are deemed responders per**	Updated based on protocol amendment 3, Synopsis, Methodology

		the definition in Section 8.1.1 after the 20th patient is censored, is alive and progression-free at the Month 6 assessment in the Safety Population, enrollment will continue to Stage 2.	
Section 4.3.2, Per Protocol (PP) Population	~~This analyses~~ population will be used for analysis of primary and secondary efficacy endpoints.	**The analysis** population will be used for analysis of primary and secondary efficacy endpoints.	Grammar updated
Section 4.3.3, By Treatment Cycle Population		Added: **4.3.3. By Treatment Cycle Population** **The by treatment cycle population consist of all patients who completed at least a 3 cycles of combination treatment.** **The by treatment cycle population will be used for analysis of all efficacy endpoints as exploratory analysis as well as all AE outputs.**	Updated based on protocol amendment 3, Section 4.3 Exploratory Objectives
Section 4.3.5, PK Population	The PK population will consist of all patients treated with study drug and who have adequate samples taken to reliably estimate at least 1 of the PK parameters of interest. Determination of the PK population will be reviewed after all PK concentration data are made available.	The PK population will consist of all patients treated with **at least 1 dose of** study drug and who have adequate samples taken to reliably estimate at least 1 of the PK parameters of interest. Determination of the PK population will be reviewed after all PK concentration data are made available.	Updated based on protocol amendment 3, Section 10.2, Analysis Populations
Section 6.1, Demographics	The following variables will be summarized: 1. Continuous baseline demographic variables:	1. Continuous baseline demographic variables: • Age at time of consent (years) • Height (in inches) • **Weight (in kg)**	Specified all subgroup categories based on demographic data

	• Age at time of consent (years) • Height (in inches) 2. Categorical baseline demographic variables: • Sex (male, female) • Childbearing potential (if female) (Yes, No) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • Race (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)	• **BMI (in kg/m2)** 2. Categorical baseline demographic variables: • **Age: <Median and ≥ Median age** • Sex (male, female) • Childbearing potential (if female) (Yes, No) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • Race: **All races** (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other) **and White vs Non-white**	
Section 6.2, Baseline Disease Characteristics	Baseline values from the parameters below, but not limited to, will be tabulated: ... Duration of cancer at study entry is defined as the date of inform consent minus the date of diagnosis and will be presented in months. Incomplete dates will be derived following the same rules for medical history. Baseline disease characteristics will be presented in a listing.	Baseline values from the parameters below, but not limited to, will be tabulated: ... • **Patients with changes in liver function tests** • **Patients with Biliary stents** • **Prior therapy** Duration of cancer at study entry is defined as the date of inform consent minus the date of diagnosis **+ 1** and will be presented in months. Incomplete dates will be derived following the same rules for medical history. **Patients with changes in liver function tests will be identified using "Drug related hepatic disorders - comprehensive search" PT coding terms based on AE records. Patients with Biliary stents will be identified using**	Specified all subgroup categories and definitions based on baseline disease characteristics data

		"Biliary stent", "Biliary Tract stent", "Bile duct stent" from Medical history term. Patients with prior therapy will be identified using the leading question "Is Condition or Term associated with BTC?" in Medical history CRF page. Baseline disease characteristics will be **summarized in table and also will be** presented in a listing. **C1D1 images or images being obtained within 6 weeks prior to Day 1, or whichever images were closest in date to C1D1 are submitted to BICR for establishment of Baseline.**	
Section 6.5, Subgroups		Added: **6.5 Subgroups** **The following subgroups will be defined:** • CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI	Added subgroup section and definition here.

		[redacted] CCI **the change from baseline at Month 6, Month 12 and EOS will be categorized into "decrease >= 30%" and "decrease < 30%".** **• body weight – Subgroup categories: <Median and ≥ Median baseline weight** **• serum albumin - Subgroup categories: Normal and Abnormal baseline albumin** **Demographics and disease characteristics will be considered as subgroups including:** **• major demographic** **o Age: <Median and ≥ Median age** **o Sex: Male vs Female** **o Race: White vs Non-white** **• Subgroup analyses in:** **o Patients with changes in liver function tests** **o Patients with Biliary stents** **o Location of disease (Histology: intrahepatic, extrahepatic, or gallbladder)** **o Prior therapy** **o ECOG performance status** **Subgroups mentioned in the protocol based on correlation between Baseline neutrophil:lymphocyte ratio and OS, prognostic subgroups, extent of disease are not planned but might be performed upon reviewing the data. Such analyses**	

		will be defined in the Clinical Study Report. **Patients with changes in liver function tests will be identified using "Drug related hepatic disorders - comprehensive search" PT coding terms based on AE records. Patients with Biliary stents will be identified using "Biliary stent", "Biliary Tract stent", "Bile duct stent" from Medical history term. Patients with prior therapy will be identified using the leading question "Is Condition or Term associated with BTC?" in Medical history CRF page.** **Subgroup analyses of PFS, OS, ORR, and DCR will be evaluated for exploratory endpoints.**	
Section 7.3.1, Extent of Exposure	• Cumulative dose (mg) is defined as the sum of all doses taken per drug during the treatment period for XERMELO only.	• Cumulative dose (mg) is defined as the sum of all doses taken per drug during the treatment period for XERMELO only **based on drug accountability.** … **Overall treatment duration and dose status will also be presented in the table.**	Added clarification for XERMELO cumulative dose calculation and specify the table will be summarized.
Section 7.3.2, Treatment Compliance and Modifications	• Compliance (%) defined as [(actual number of tablets taken over the study period) / (designated total number of tablets that should have been taken over the study period)] * 100 for XERMELO. Actual number of tablets taken will be calculated	• Compliance (%) defined as [(actual number of tablets taken over the study **period prior to EOT**) / (designated total number of tablets that should have been taken over the study period **prior to EOT**)] * 100 for XERMELO. Actual number of tablets taken will be calculated	Specified the XERMELO compliance calculation duration and details.

	using the dispensed and returned count from the XERMELO Dispensation CRF page. All the tablets not returned will be considered as taken by patient. Designated total number of tablets will be based on exact days patients were put under treatment cycles (250 mg tid starting on Day 1 and 500 mg tid staring on Day 8) regardless dose interruptions and/or modifications.	using the dispensed and returned count from the XERMELO Dispensation CRF page. All the tablets not returned will be considered as taken by patient. Designated total number of tablets will be based on exact days patients were put under treatment cycles (250 mg tid starting on Day 1 and 500 mg tid staring on Day 8 **in cycle 1 and 500 mg tid in cycle 2 and after**) regardless dose interruptions and/or modifications.	
Section 8.1, Primary Efficacy Analysis	Section 8.1, Primary Efficacy ~~Endpoint~~	Section 8.1, Primary Efficacy **Analysis**	
Section 8.1.1, Progression-free Survival (PFS)	A Safety physician from ~~Lexicon~~ will identify the anticancer treatments and first date of their administration from the concomitant medication records. The full event and censoring rules for deriving PFS are specified in Table 9 below.	A Safety physician from **TerSera** will identify the anticancer treatments and first date of their administration from the concomitant medication records. The full event and censoring rules for deriving PFS are specified in Table 9 below. **Cycle 10 Day 1 is considered the Month 6 timepoint and Cycle 19 Day 1 is considered the Month 12 timepoint for analysis purposes. Patients who prematurely discontinued from Treatment Period or withdrew consent from Treatment Period prior to Month 6 of the Treatment Period, will be asked to reconsent to allow for images and or imaging reports, obtained locally, to be submitted to BICR.**	Changed the sponsor name to TerSera and add details of Month 6 and Month 12 definition per protocol amendment 3

Table 9, Censoring Conventions for PFS	Treatment discontinuation for toxicity or other reasons prior to disease progression and Month 6 radiological assessment is not available	Treatment discontinuation for toxicity or other reasons **(except death)** prior to disease progression and Month 6 radiological assessment is not available	Add clarification for the exception of treatment discontinuation due to death is not considered as censored.
Section 8.1.1, Progression-free Survival (PFS)	The primary efficacy endpoint is the PFS response rate at 6 months. This is a binomial variable in which the numerator is derived as the number of patients at 6 months who are alive and event-free. Event-free means that ~~that~~ a valid radiologic assessment of disease (ie, radiological scan of the tumor) at 6 months shows that the patient has no progressive disease (PD) per RECIST 1.1 criteria. … In addition to the PFS response rate, the PFS rate at Month 6 ~~derive~~ as a function of a time-to-event outcome, and the corresponding 95% confidence interval (CI), will be presented. The Kaplan-Meier method will be used to estimate the survival function of this measure of the PFS variable.	The primary efficacy endpoint is the PFS response rate at 6 months **and scheduled cycle 10 day 1 disease assessment results will be used for this purpose.** This is a binomial variable in which the numerator is derived as the number of patients at 6 months who are alive and event-free. Event-free means that a valid radiologic assessment of disease (ie, radiological scan of the tumor) at 6 months shows that the patient has no progressive disease (PD) per RECIST 1.1 criteria. ... In addition to the PFS response rate, the PFS rate at Month 6 **derived** as a function of a time-to-event outcome, and the corresponding 95% confidence interval (CI), will be presented. The Kaplan-Meier method will be used to estimate the survival function of this measure of the PFS variable.	Clarification added based on protocol amendment 3, Synopsis, Methodology
Section 8.1.2, Sensitivity Analysis	A separate sensitivity analysis will also be performed on the PFS response rate as defined in Section 8.1.1 based on the PP population.	A separate sensitivity analysis will also be performed on the PFS response rate as defined in Section 8.1.1 based on the PP population **as well as by treatment cycle population**.	Updated based on protocol amendment 3, Section 4.1 Primary Objective

Section 8.2, Secondary Efficacy Analysis	Section 8.1, Secondary Efficacy ~~Endpoint~~	Section 8.1, Secondary Efficacy **Analysis**	
Section 8.2.1, PFS Rate at Month 12 and Median PFS		Added: **Scheduled disease assessment at cycle 19 day 1 will be used to determine PFS response rate at month 12.**	Updated based on protocol amendment 3, Synopsis, Methodology
Section 8.2.6, Change in Tumor Size		Added: **A waterfall plot will be provided of change in tumor size (as of % of baseline) from baseline to Month 6 response for all patients for whom primary lesion data are available and will be displayed based on Safety population. Associated change from baseline summary table will be also provided.**	Added per TerSera's request
Section 8.2.7, Sensitivity Analysis		Added: **A separate sensitivity analysis will also be performed on all secondary efficacy tables as defined in Section 8.2 based on the PP population as well as by treatment cycle population.**	Updated based on protocol amendment 3, Section 4.3 Exploratory Objectives
Section 9.2, Subgroup Analysis	Subgroup analyses of PFS, OS, ORR, and DCR may be performed using both BICR and local radiologist's assessment, based on categorical ~~group of Baseline in:~~ • CCI CCI CCI CCI	Subgroup analyses of PFS, OS, ORR, and DCR may be performed using both BICR and local radiologist's assessment, based on categorical **subgroup group variables. Subgroup definition details are specified in Section 6.5.**	Moved the subgroup definition to section 6.5.

	~~Subgroup analyses mentioned in the protocol based on correlation between Baseline neutrophil:lymphocyte ratio and OS, the primary tumor site, prior therapy(ies), performance status, prognostic subgroups, extent of disease are not planned but might be performed upon reviewing the data. After reviewing the data, additional subgroup analysis may be performed. Such analyses will be defined in the Clinical Study Report.~~		
Section 9.3, Sensitivity Analysis		Added: **9.3 Sensitivity Analysis** **All efficacy analyses will be also conducted based on the PP population as well as by treatment cycle population.**	Added Sensitivity Analysis section under exploratory analysis per TerSera's request
Section 10, Safety Analysis	Safety and tolerability will be evaluated through the collection and review of treatment-emergent adverse events (TEAEs), as graded by CTCAE v5.0, vital signs measurement, 12-lead electrocardiogram (ECG) findings, physical examination (PE) findings, and clinical laboratory parameters (chemistry, hematology, and urinalysis) including changes from Baseline and frequency of values meeting CTCAE Grades >1, CTCAE Grades 3/4 separately. All	Safety and tolerability will be evaluated through the collection and review of treatment-emergent adverse events (TEAEs), as graded by CTCAE v5.0, vital signs measurement, 12-lead electrocardiogram (ECG) findings, physical examination (PE) findings, and clinical laboratory parameters (chemistry, hematology, and urinalysis) including changes from Baseline and frequency of values meeting CTCAE Grades >1, CTCAE Grades 3/4 separately. **In addition, shift table analyses will be applied to the laboratory data.** All	Added clarification for lab shift table. Added AE additional analyses per TerSera's request

	summaries will be performed using the Safety population. ... Summaries will be prepared by study time point. All safety data will be listed by patient.	summaries will be performed using the Safety population. ... Summaries will be prepared by study time point. **Adverse events will also be prepared by PP population as well as by treatment cycle population. Adverse events will also be displayed by study drug cycle based on Safety population.** All safety data will be listed by patient.	
Section 10.1, Adverse Events		Added: • **TEAEs that leading to treatment reduction by SOC and PT** • **TEAEs that leading to XERMELO reduction by SOC and PT** • **TEAEs that leading to XERMELO interruption by SOC and PT** • TEAEs with severity grade ≥ 1 by SOC and PT • TEAEs with severity grade ≥ 2 by SOC and PT • TEAEs with severity grade 3 and 4 by SOC and PT • Adverse events of special interest (AESI) by SOC and PT … **All AE tables will be displayed based on safety population, PP population as well as by treatment cycle population. All AE tables by study drug cycle will also be displayed based on safety population.**	Added AE additional analyses per TerSera's request
Section 10.1.1, Incidence of Adverse Events	An overall summary of TEAEs will be presented in a table and will	An overall summary of TEAEs will be presented in a table and will include the	Added AE additional

	include the number and incidence of patients with any TEAE, number of TEAEs, patients with serious TEAEs, patients with severe TEAE (≧ Grade 3), patients that discontinued from study due to TEAEs, and deaths. In addition, the table will include the number and percentage of patients in each category of severity (ie, Grade 1 to Grade 5) for all TEAEs and the number and percentage of patients in each category of relationship to each study drug (ie, "Related" and "Not Related").	number and incidence of patients with any TEAE, number of TEAEs, patients with serious TEAEs, patients with severe TEAE (≧ Grade 3), patients that discontinued from study due to TEAEs, **TEAE leading to dose reduction, TEAE leading to discontinuation from treatment,** and deaths. In addition, the table will include the number and percentage of patients in each category of severity (ie, Grade 1 to Grade 5) for all TEAEs and the number and percentage of patients in each category of relationship to each study drug (ie, "Related" and "Not Related").	analyses per TerSera's request
Section 10.1.9, Adverse Events Leading to Dose Reduction		New Section	Added new section per TerSera's request
Section 10.1.10, Adverse Events Leading to XERMELO Reduction		New Section	Added new section per TerSera's request
Section 10.1.11, Adverse Events Leading to XERMELO Interruption		New Section	Added new section per TerSera's request
Section 10.1.12, Adverse Events of Special Interest	Section ~~10.1.9.~~Adverse Events of Special Interest	Section **10.1.12.**Adverse Events of Special Interest	
Section 10.1.13, Deaths	Section ~~10.1.10.~~Deaths	Section **10.1.13.** Deaths	
Section 10.3, Vital Sign Measurements		Added: **For weight, the proportions with stable weight, weight gain, weight loss will also be summarized. Stable weight is defined as a change from baseline to week 24 of less than 3%. Weight gain is an increase**	Added additional analyses per TerSera's request

		of at least 3%, and weight loss is a reduction of at least 3%.	
Section 12, Pharmacodynamics	Actual and change from Baseline for [redacted] will be summarized at Month 6, Month 12, and EOS using descriptive statistics.	Actual and change from Baseline for [redacted] will be summarized at Month 6, Month 12, and EOS using descriptive statistics **and 1-sample t-tests may be performed to test for significance using a 5% level of significance**.	Added clarification based on protocol section 10.4.1, Efficacy Analyses
Section 13, Interim Analysis	~~An interim analysis will be performed at Stage 1 once 20 patients are accrued, treated with study medication, and either have a 6-month scan for determination of PFS response or stopped the study early regardless of having a scan for disease assessment. Patients beyond the initial 20 patient cohort will be allowed to enroll while the data accumulates for the Stage 1 analysis. If fewer than 12 PFS responders are observed at Stage 1, patient accrual is to stop, and the study regimen declared "inactive". In the case that 12 or more PFS responders are observed at Stage 1, patient enrollment will continue to the maximum sample size of 53 patients. If at the end of Stage 2 the number of PFS responders at Month 6 exceeds 34 patients, then the null hypothesis will be rejected, and the study treatment labeled a "success". Should an excessive number of PFS~~	Added: **Stage 1 analysis** **Stage 1 enrollment will include a Safety Run-in cohort. Safety and tolerability data of the combination treatment from the first 6 patients who complete at least 21 days of safety follow-up after the first dose of combination treatment will be evaluated. During this review, Stage 1 enrollment will continue. It is anticipated that a total of 20 patients will participate in Stage 1. If there are no clinically significant or unresolved Grade 3 or higher toxicities considered related to the study drug and if of 12 (60%) or more of the 20 patients enrolled are deemed PFS responders in the Safety population, enrollment will continue to Stage 2. In addition, selected efficacy will be assessed in the per-protocol population and by treatment cycle.** **Stage (1 + 2) analysis and Interim Analyses:**	Updated based on protocol amendment 3, Section 10.4.7, Interim Analysis

	~~response "failures" occur at any time over the course of the study such that the sampling rule cannot be successfully achieved at either Stage, consideration will be given to stop patient accrual at that time.~~	**Formal statistical interim analyses will be performed during this study as follows:** • **Interim analysis 1 : Conducted in Patients included in the Stage 1 analysis (first 20 patients enrolled) and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data.** • **Interim analysis 2 added to (Stage 1+2) 6 month analysis : Conducted after all 53 Patients (Stage 1 + Stage 2) complete the Month 6 visit, and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle population.** • **Interim Analysis 3 added to (Stage 1+2) 12 month analysis: Conducted after all 53 Patients (Stage 1 + Stage 2) complete the Month 12 visit, and will include safety, efficacy (PFS responder rate), pharmacodynamic (biomarker) data and analysis by treatment cycle population.**	
Section 14, References	1. Lexicon LX16061207BTC Protocol: A Phase 2, Multicenter, Open-label, Safety and Efficacy Study of XERMELO® (Telotristat Ethyl) plus First-line Chemotherapy in Patients with Locally Advanced, Unresectable, Recurrent or	1. **TerSera LX1606.1-207-BTC** Protocol: A Phase 2, Multicenter, Open-label, Safety and Efficacy Study of XERMELO® (Telotristat Ethyl) plus First-line Chemotherapy in Patients with Locally Advanced, Unresectable,	updated based on protocol amendment 3

	Metastatic Biliary Tract Cancer (BTC)	Recurrent or Metastatic Biliary Tract Cancer (BTC)	
Section 15.1, Schedule of Study Procedures		Update Schedule of Study Procedures table and footnote based on protocol amendment 3.	updated based on protocol amendment 3
Section 15.5, Visit Cycles and Analysis Timepoints		Added: **Table 11 Visit Cycles and Analysis Timepoints**	Added new table per TerSera's request
Section 15.6, Detailed Summary of SAP Changes		New Section	