Statistical Analysis Plan

Study Title:	A Randomized Controlled, Open label, Adaptive Phase-3 Trial to Evaluate Safety and Efficacy of EndoTAG-1 Plus Gemcitabine versus Gemcitabine alone in Patients with Measurable Locally Advanced and/or Metastatic Adenocarcinoma of the Pancreas Failed on FOLFIRINOX Treatment
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REVISION HISTORY

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3.0	28-Jan-2021	Changes made based on FDA comments IND 106057 SynCore Advice-Information Request IND_SDN36 19Sep2020 (Reference ID: 4673002)
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1. LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviations	Description
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
CA 19-9	Carbohydrate Antigen 19-9
CDE	Common Data Elements
CDISC	Clinical Data Interchange Standards Consortium
CDMS	Clinical Data Management System
CFB	Change From Baseline
CI	Confidence Interval
cm	centimeter
CONSORT	CONsolidated Standards Of Reporting Trials
CP	Conditional Power
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DR	Duration of Response
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC-QLQ-PAN26	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Pancreatic Module
FBC	Full Blood Count

FDA	Food and Drug Administration
H	High
HCT	Hematocrit
HR	Heart Rate
IA	Interim Analysis
ICH	International Conference on Harmonisation
INR	Internation Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
kg	kilogram
L	Low
m	meter
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NINDS	National Institute of Neurological Disorders and Stroke
ODS	Output Delivery System
OR	Objective Response
OS	Overall Survival
PCFB	Percent Change From Baseline
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PT	Prothrombin Time
QC	Quality Control
QoL	Quality of Life
Qs	Questions

RBC	Red Blood Cell
RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressue
SD	Standard Deviation
SD	Stable Disease
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TLFs	Tables, Listings and Figures
WBC	White Blood Cell
WHODrug	World Health Organization Drug Dictionary

2. INTRODUCTION

This Statistical Analysis Plan (SAP) is prepared to provide a more technical and detailed elaboration of the principal statistical features stated in the protocol. The SAP will ensure that the tables, listings, and figures that will be produced and statistical methods that will be used are complete and accurate and will allow valid conclusions to be drawn. In the development of this SAP, the following documents were used:

- CT 4006 (version 4.2), 28 Jan 2021

The principles in the following guidance documents are followed in preparation of this SAP:

- International Conference on Harmonisation (ICH) E3 (1995): Structure and Content of Clinical Study Reports
- ICH E6 R2 (2016): Guideline for Good Clinical Practice
- ICH E9 (1998): Statistical Principles for Clinical Trials

In the event that a discrepancy is found between the descriptions in the statistical section of the protocol and this document, the description in this document supersedes the descriptions in the statistical section of the protocol.

3. STUDY OVERVIEW

EndoTAG-1 is a novel formulation of cationic liposomes for the treatment of solid tumors, carrying paclitaxel embedded in the liposome membrane. Cationic liposomes are known to bind and internalize at tumor endothelial cells after intravenous administration, which is the basis for the new mode of action of EndoTAG-1. Using a cationic liposome formulation, the cytostatic and cytotoxic activities of paclitaxel are targeted to the activated tumor endothelial cells. Therefore, in contrast to conventional chemotherapy aiming at tumor-cell toxicity, EndoTAG-1 specifically displays antivascular and antiangiogenic activity.

Based on the results of preclinical studies and clinical phase 1/2 studies and its new therapeutic concept, EndoTAG-1 represents a promising candidate for the treatment of solid malignancies, both for taxane-sensitive and taxane-insensitive tumors.

Pancreatic cancer, which is the 4th leading cause of cancer death in the United States (Jemal et al. 2008), is an indication with high need for improvement of systemic therapy. Less than 20% of pancreatic cancer patients are diagnosed with resectable and potentially curable disease while the vast majority of patients have advanced disease at the time of diagnosis with a median survival of approximately 6 months.

FOLFIRINOX regimen is the standard first-line treatment for pancreatic cancer patients with good performance status. However, the optimal management strategy for patients who fail initial FOLFIRINOX remains undefined. There is still no standard of care in second-line therapy for patients with disease progression.

Gemcitabine has been the standard systemic therapy for unresectable pancreatic cancer for the last decade, though 1-year survival rates ranging around 18% are still unsatisfactory (Burris et al. 1997; Moore et al. 2007). Numerous trials have aimed to demonstrate superiority of combinations of gemcitabine with other chemotherapeutics or targeted agents with disappointing results.

Results of a controlled, randomized Phase 2 clinical trial comprising 200 patients indicate a considerable survival benefit for patients with advanced pancreatic cancer treated with EndoTAG-1 in combination with gemcitabine compared to gemcitabine monotherapy.

The aim of this adaptive Phase 3 trial is to show a statistically significant superiority of EndoTAG-1 in combination with gemcitabine compared to gemcitabine monotherapy in patients with locally advanced/metastatic pancreatic cancer after FOLFIRINOX failure.

3.1 Study Objectives

The objective of the study is to assess the safety and efficacy of a combination therapy of EndoTAG-1 plus gemcitabine vs. gemcitabine monotherapy in patients with locally advanced and/or metastatic

adenocarcinoma of the pancreas eligible for second-line therapy after failing first-line therapy with FOLFIRINOX.

3.1.1 Efficacy Objectives

To assess the efficacy of twice weekly infusions of EndoTAG-1 with weekly infusions of gemcitabine versus gemcitabine monotherapy according to:

- Assessment of survival (overall survival [OS], progression-free survival [PFS])
- Tumor response evaluation via Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1)

3.1.2 Safety Objectives

To assess the safety of twice weekly infusions of EndoTAG-1 with weekly infusions of gemcitabine versus gemcitabine monotherapy according to:

- Incidence and percentage of subjects with treatment-emergent adverse events (TEAEs)
- Laboratory abnormalities (hematology, coagulation parameters, clinical chemistry)
- Dose reductions, pausing, and/or discontinuation of EndoTAG-1 and/or gemcitabine

3.2 Study Design

This is a randomized controlled, open label, adaptive phase-3 study to evaluate the safety and efficacy of a combination regimen of twice weekly infusions of EndoTAG-1 (Lipid Complexed Paclitaxel) with weekly administration of gemcitabine compared with gemcitabine monotherapy in subjects with measurable locally advanced and/or metastatic adenocarcinoma of the pancreas who are eligible for second-line therapy after failing first-line therapy with FOLFIRINOX.

Eligible subjects will be randomized to one of the two treatment arms:

- Arm A: Treatment with EndoTAG-1 22 mg/m^2 twice weekly plus gemcitabine 1000mg/m^2 once weekly, for 1 cycle (8 weeks) consisting of 3 weeks and 1 week rest followed by 3 weeks of treatment and 1 week rest until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent. Subjects will be eligible for continuing treatment beyond first cycle with 3 weeks of treatment and 1 week rest in absence of disease progression or unacceptable toxicity.
- Arm B: Treatment with gemcitabine 1000mg/m^2 once weekly, for 1 cycle (8 weeks) consisting of 3 weeks and 1 week rest followed by 3 weeks of treatment and 1 week rest until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent. Subjects will be eligible for continuing treatment beyond first cycle with 3 weeks of treatment and 1 week rest in absence of disease progression or unacceptable toxicity.

The randomization will be stratified by:

- Subjects with locally advanced vs metastatic pancreatic cancer
- Subjects with Eastern Cooperative Oncology Group (ECOG) performance status 0 vs 1

The first treatment cycle will last at least 8 weeks and include 3 weeks of treatment and 1 week rest followed by 3 weeks of treatment and 1 week rest. Subjects may continue to receive additional cycles of therapy until progressive disease or intolerable toxicity as per clinical judgment of the Investigator.

Tumor response according to RECIST (version 1.1; Eisenhauer et al. 2009) will be evaluated on a scheduled basis every 8 weeks (±3 days) from randomization (regardless of the timing of treatment cycles) until disease progression is documented or until the cut-off date of the study, whichever comes earlier. Subjects will be monitored regularly for safety parameters, pain and quality of life.

After completing treatment, subjects who are not diagnosed with progressive disease (PD) will attend up to 6 Follow-up Visits every 8 weeks for 48 weeks, following which subjects will be followed-up by telephone every 8 weeks for survival. Subjects who experienced PD during Treatment Phase will undergo only one safety follow-up visit (4-8 weeks after the EOT visit), and then enter phone follow-up directly. Follow-up visits will be performed for the evaluation of survival status, safety parameters, QoL (EORTC QLQ-C30 and EORTC PAN-26) and administration of other anti-tumor treatment until death or end of the study, whichever comes first.

Anti-tumor therapy after termination of study treatment will be at the discretion of the Investigator. An Interim Analysis (IA) will be conducted when approximately 101 deaths have occurred on study.

The cut-off date for the final analysis will be 12 months after the last subject was randomized or the last subject alive has been followed up for at least 48 weeks, whatever applies first. Subjects being still under treatment with study medication at this cut-off date will enter the extension phase of this trial. These subjects will be followed up until 28 days after the last administration of study medication.

A Data and Safety Monitoring Board (DSMB), composed of independent representatives, will be in charge of reviewing the accrual, baseline, and safety data at periodic intervals. Representatives of the Sponsor will serve only as coordinating members of the committee, without having full member responsibilities or privileges.

The Schedule of Assessments can be found in Table 1-1 and Table 1-2 in Section 3.2.3

3.2.1 Sample Size Considerations

A total of 218 subjects will be enrolled and randomized in a 1:1 ratio to Arm A (EndoTAG-1 plus gemcitabine) and Arm B (gemcitabine monotherapy). The sample size is event-driven to allow for collection of a pre-specified number of primary efficacy outcomes. Based on the sample size

calculation, the primary endpoint analysis for overall survival will require 167 events (deaths) from 196 subjects. The primary endpoint analysis for progression-free survival will require 169 events (disease progression) from 182 subjects.

This sample size is sufficient to detect a 40% reduction of overall survival in the risk of death in Arm A, as compared with Arm B (hazard ratio, 0.60) using a 2-sided log-rank test with 90% power and an overall significance level of 0.05 two sided test.

This sample size is also sufficient to detect a 35% reduction of progression-free survival in the risk of death in Arm A, as compared with Arm B (hazard ratio, 0.647) using a 2-sided log-rank test with more than 80% power and an overall significance level of 0.05 two sided test.

Sample size estimation for overall survival is depicted in Figure 1, total sample size requirement vs. the median survival time (month) in the treatment arm. Sample size is estimated using PASS (15) sample size software.

Sample size estimation for progression-free survival is depicted in Figure 2, total sample size requirement vs. the median survival time (month) in the treatment arm. Sample size is estimated using PASS (15) sample size software.

It is anticipated that there would be about 10% dropout in this study, to accommodate for the dropouts a total of 218 subjects would be randomized. The overall survival assumption for the sample size are based on published literature data comparing therapeutic effect of gemcitabine monotherapy and gemcitabine combination regimen on patients with advanced pancreatic cancer after previous FOLFIRINOX treatment. The hazard ratio for death of 0.60 with median overall survival of 4.4 months for gemcitabine monotherapy (Conroy et al. 2011) and 7.3 months for gemcitabine + paclitaxel combination (Portal et al. 2015) was used for the sample size calculation.

The progression-free survival assumption for the sample size are based on hazard ratio of 0.647 with median progression-free survival of 3.3 months for gemcitabine monotherapy (Conroy et al. 2011) and 5.1 months for gemcitabine + paclitaxel combination (Portal et al. 2015) was used for the sample size calculation.

Figure 1: Overall Survival Sample Size Plot: Total Sample size Requirement vs. the Median Survival Time (month) in the Treatment Arm A.

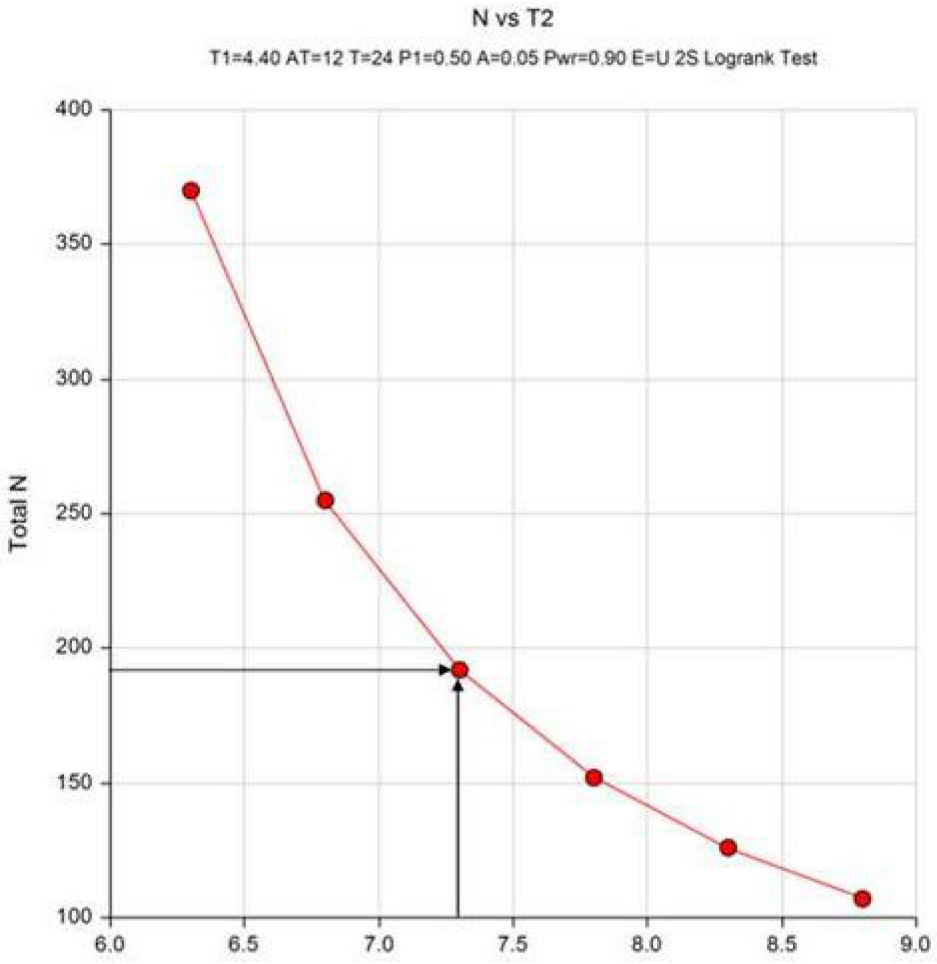
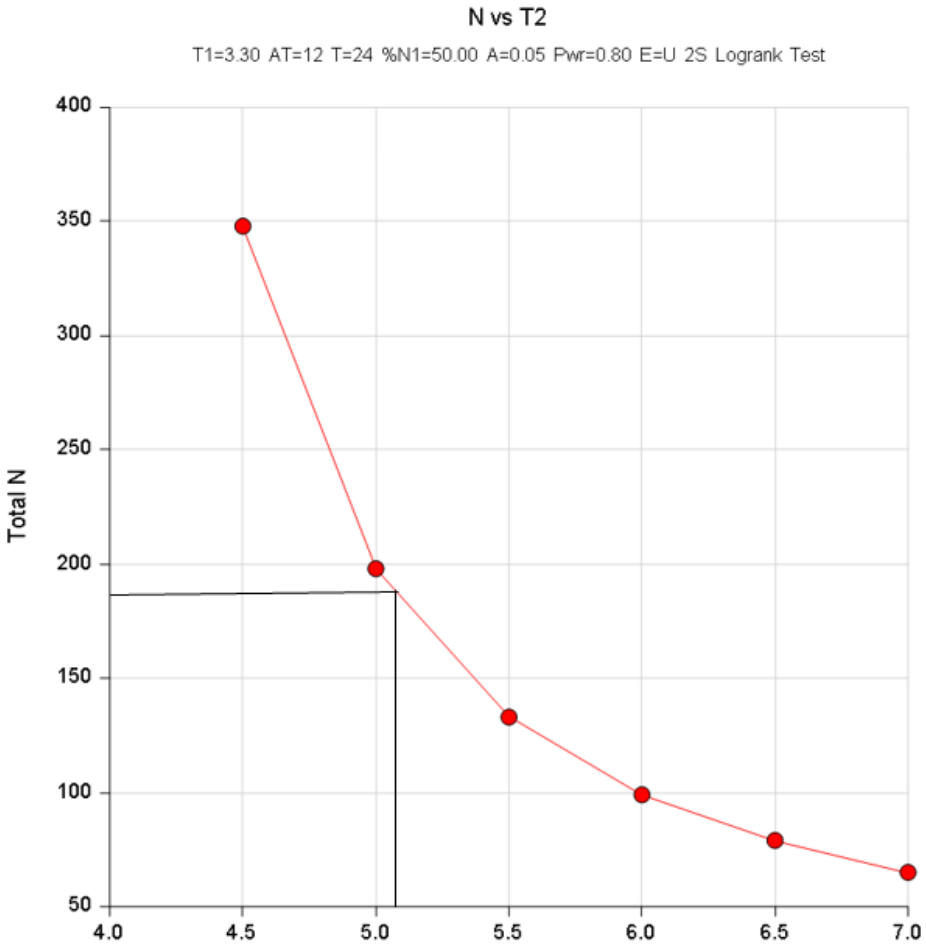


Figure 2: Progression-Free Survival Sample Size Plot: Total Sample size Requirement vs. the Median Survival Time (month) in the Treatment Arm A.



During the interim analysis, the sample size will be re-evaluated. Detals of this procedure are given in Section 5.4.

3.2.2 **Randomization**

Subjects who are eligible to participate in the trial will be centrally randomized to receive either Arm A (EndoTAG-1 and gemcitabine) or Arm B (gemcitabine alone) in a 1:1 ratio using a stratified block randomization scheme. The stratification variables are the extent of disease (subjects with locally advanced and metastatic pancreatic cancer) and the performance status (ECOG performance status 0 and 1). Within each stratum, subjects will be allocated with equal probability to either treatment in Arm A or treatment in Arm B and the randomization system will be set up in such a way that there is a 1:1 balance between the treatment groups from the different strata.

The randomization schedule generated will include sufficient assignments to randomize the maximum number of subjects possible in the case of sample size re-estimation after the interim analysis (Section 5.4).

As this is an open label study, all study personnel will have knowledge of the treatment assignments after randomization and throughout the study. To avoid any susceptible selection bias, a stratified block randomization scheme with a mixed block size will be used and the blocks will be blinded until trial closure to all research personnel except the block generating statistician. The master randomization lists containing the treatment assignments will not be released to any study personnel prior to final database lock except for the DSMB meetings and at the time of the interim analysis.

3.2.3 **Study Assessments Schedules**

Study assessments are described in detail in the protocol, and summarized below in Table 1-1 and Table 1-2.

Table 1-1: Schedule of Assessments – Screening and Treatment Phase

	Screening Phase	Treatment Phase First cycle													
VISIT NUMBER	SV	1[1]	1 G[2]	2	2 G	3	3 G	rest	5	5 G	6	6 G	7	7 G	8[3]/ EOT
DAY	Within 14 days from D1	Wk 1 (D1)	Wk 1 (D4)	Wk 2 (D8)	Wk 2 (D11)	Wk3 (D15)	Wk 3 (D18)	Wk 4	Wk 5 (D29)	Wk 5 (D32)	Wk 6 (D36)	Wk 6 (D39)	Wk 7 (D43)	Wk 7 (D46)	Wk 8 (D53)
Informed consent	X														
In-/Exclusion criteria	X														
Disease history	X														
Medical history	X														
Demographic data	X														
ECOG	X														X
Physical examination	X	X	X		X		X			X		X		X	X
Vital signs	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Laboratory assessments:															
Hematology	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Clinical chemistry	X	X	X						X	X					X
Coagulation parameter	X	X	X		X		X			X		X		X	
CA 19-9	X														X
Pregnancy test	X														X
Urinalysis	X														X
PK blood sample Collection		X	X	X		X			X				X		
QoL questionnaires	X														X
Tumor imaging	X														X[4]
ECG	X														X
Adverse events		X	X	X	X	X	X		X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Randomization	X	X													
Treatment Group A (EndoTAG-1 + gemcitabine)		X	X	X	X	X	X		X	X	X	X	X	X	
Treatment Group B (gemcitabine monotherapy)			X		X		X			X		X		X	

1 Visit without suffix "G": administration of EndoTAG-1 only; visit applies only to subjects of treatment group A
2 Visits with suffix "G": administration of gemcitabine (Treatment Groups A and B) +/- EndoTAG-1 (Treatment group A)
3 End of Cycle visit 4 Imaging every 8 weeks irrespective of timing of treatment cycle

Table 1-2 Schedule of Assessments – Subsequent Treatment Cycles and Follow-up Phase

	Treatment Phase Subsequent cycles														Follow-up Phase	
VISIT NUMBER	1[1]	1 G[2]	2	2 G	3	3 G	rest	5	5 G	6	6 G	7	7 G	8[3]/EOT	Follow-up visit 1	Subsequent Follow-up visits
DAY	Wk 1 (D1)	Wk 1 (D4)	Wk 2 (D8)	Wk 2 (D11)	Wk3 (D15)	Wk 3 (D18)	Wk4	Wk 5 (D29)	Wk 5 (D32)	Wk 6 (D36)	Wk 6 (D39)	Wk 7 (D43)	Wk 7 (D46)	Wk 8 (D53)	8 weeks after last study treatment[5]	until end of study[5]
ECOG	X													X	X	
Physical examination		X		X		X			X		X		X	X	X	
Vital signs	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Laboratory assessments:																
Hematology	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Clinical Chemistry	X	X						X	X					X	X	
Coagulation parameter		X		X		X			X		X		X		X	
CA 19-9														X	X	
Pregnancy test														X	X	
Urinalysis														X	X	
QoL questionnaires														X	X	
Tumor imaging														X[4]	X[4]	
ECG														X	X	
Adverse events	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Treatment Group A (EndoTAG-1 + gemcitabine)	X	X	X	X	X	X		X	X	X	X	X	X			
Treatment Group B (gemcitabine monotherapy)		X		X		X			X		X		X			
Change in tumor therapy															X	X
Survival															X	X

[1] Visit without suffix "G": administration of EndoTAG-1 only; visit applies only to subjects of treatment group A
[2] Visits with suffix "G": administration of gemcitabine (Treatment Groups A and B) +/- EndoTAG-1 (Treatment group A)
[3] End of Cycle visit [4] Imaging every 8 weeks irrespective of timing of treatment cycle [5] Follow up visits will be performed at every 8-week interval

4. STUDY ENDPOINTS AND DEFINITIONS

4.1 Primary Efficacy Endpoint

- Overall survival (OS)

Overall survival time is defined as time from randomization to death from any cause or last day known to be alive.

- Progression Free Survival (PFS)

Progression Free Survival time is defined as the time from randomization to either first observation of progressive disease or occurrence of death.

4.2 Secondary Efficacy Endpoints

The following are the secondary efficacy endpoints:

- Percentage of subjects with Objective Response (OR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1)
- Duration of Response (DR)
- Percentage of subjects with disease control according to RECIST v.1.1
- Serum Carbohydrate Antigen 19-9 (CA 19-9) response rate

4.3 Exploratory Endpoints

- Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score
- Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score

4.4 Safety Endpoints

The following are the endpoints that will be used to assess safety:

- Incidence and severity of treatment-emergent adverse events (TEAEs), including serious adverse events and adverse events resulting in permanent discontinuation of protocol-defined therapy.
- Changes in selected laboratory test results (i.e.,
    - Serum chemistry including urea, serum creatinine, sodium, potassium, chloride, bicarbonate, glucose, bilirubin, albumin, ALT, AST, ALP, total protein; and
    - Full blood count (FBC) including hemoglobin, hematocrit, RBC count, Platelets count, total leukocyte count, differential leukocyte count and absolute neutrophil count)
- Changes in vital signs including systolic and diastolic blood pressure and pulse
- Changes in electrocardiogram (ECG) results
- Changes in physical examination results

4.5 Definitions

4.5.1 Study Day

For purposes of describing days on study drug in data listings, data will be assigned a study day relative to the first dose of the first cycle of the Treatment Phase (for Arm A, where a subject receives first administration EndoTAG-1 + gemcitabine [listed as first cycle D1 in Table 1-1] and for Arm B, where a subject receives the first administration of gemcitabine monotherapy [listed as first cycle D4 in Table 1-1]). This day will be known as "First Cycle First Dose." A given visit's Study Day will be assigned according to the following rules (this numbering of days differs from the "Day" as described in the Tables 1-1 and 1-2):

For events that occurred up to and including First Cycle First Dose:

Study Day = Visit date – date of First Cycle First Dose + 1

For events prior to First Cycle First Dose:

Study Day = Visit date – date of First Cycle First Dose

Visit numbers as designated on the study eCRFs (Electronic Case Report Forms) will be used. For selected parameters, visit windows will also be calculated for use in descriptive statistics by time.

4.5.2 Baseline and Change from Baseline

Baseline assessments for efficacy and safety endpoints will be identified in Section 6.2 and 6.3, respectively.

Unless indicated otherwise, change from baseline (CFB) will be calculated as follows:

CFB = Value at Visit - Baseline

Percent change from baseline (PCFB) will be calculated as follows:

PCFB (%) = 100*(Value at Visit - Baseline)/Baseline

5. STATISTICAL ANALYSIS GENERAL CONSIDERATIONS

5.1 Analysis Populations

Screened Population: The Screened Population will include all subjects who signed the informed consent form and were screened for participation in this study. This population will be used when describing disposition in the study.

Intent-to-Treat Population: The Intent-to-Treat (ITT) population is defined as all subjects randomized, regardless of actual treatment received. The ITT population will be the primary population for the analysis of primary, secondary and exploratory endpoints.

Per Protocol Population: The Per Protocol (PP) population is defined as the set of subjects who meet the ITT population requirements, and were not associated with a major protocol violation. This population will be identified before the database lock.

The PP analysis of primary and secondary endpoints will be considered supportive.

Safety Population:

The Safety Population is defined as any subject receiving any treatment after randomization. For Arm A, this consists of subjects that received any portion of the first administration EndoTAG-1 + gemcitabine. For Arm B, this consists of subjects that received any portion of the first administration of gemcitabine monotherapy. This population will be used for the analysis of all safety endpoints.

5.2 *P*-Values

To maintain the trial-wise Type I error rate at 0.05, a hierarchical test procedure with fixed sequence will be used for the two primary endpoints and the secondary endpoints. The order of the endpoints is outlined in Section 6.2. Each subsequent endpoint will not be tested unless the previous endpoint analysis in the hierarchy has rejected the null hypothesis. If an analysis of an endpoint fails to reject the null hypothesis, then no further analyses will be performed. All secondary endpoints, if tested, will use a two-sided analysis at an α=0.05 significance level.

5.3 Procedures for Handling Missing Data

For categorical secondary efficacy endpoints, if a subject died while on-study, the endpoint will be imputed as a failure. Details are in the respective subsections in Section 6.2. Unless otherwise noted, no imputation of other endpoints or safety data will occur.

5.4 Interim Analysis

A single, pre-planned Interim Analysis (IA) will be conducted when approximately 101 subjects have died (60% of the expected 167 events) for the overall survival primary endpoint.

The results of the IA will be reviewed by an independent Data Safety and Monitoring Board (DSMB) who will assess the data for both safety (for the purposes of continuing the trial) and efficacy (for the purposes of sample size re-estimation). The DSMB responsibilities will be further elaborated in the DSMB charter. The DSMB will approve continuation of the study and recommend the sample size for remainder of the study.

5.4.1 Purpose of the Interim Analysis

The objectives of the interim analysis are to:

- Evaluate the safety of EndoTAG-1 plus gemcitabine in prolonging Overall Survival (OS) and Progression Free Survival (PFS) of subjects with locally advanced and/or metastatic adenocarcinoma of the pancreas eligible for second-line therapy after failing first-line therapy with FOLFIRINOX.
- Determine if it is necessary to evaluate the original sample size assumptions and maintain study power using adaptive design for sample size reassessment.

5.4.2 Safety Review

At the time of the interim safety data review, all the data to be used along with the treatment assignment of each randomized subject will be given to the independent statistician. Using this data, the independent statistician will prepare descriptive summary and by subject listings of baseline and safety data including demographics, adverse events, serious adverse events, laboratory findings, physical examinations, vital signs, and ECG.

5.4.3 Adaptive Design: Re-estimation of Sample Size

At the time of Interim Analysis, all the data to be used in the interim analysis along with the treatment assignment of each randomized subject will be given to the independent statistician. Using this data, the independent statistician will calculate the following metrics in addition to all the safety data that is to be prepared for the safety review:

1. For the calculation of the conditional power:
    a. Proportion of subjects randomized to each Arm at the time of interim analysis
    b. The test statistic computed from the observed data using Cox proportional hazards model outlined in the Primary Efficacy Analysis Section 6.2.1
    c. The number of events at the time of the interim analysis

2. For the re-estimation of the sample size, if necessary per Section 5.4.3.2:
    a. The median overall survival (OS) and median progression free survival (PFS) in Arm A and the observed number of subjects in the group, calculated using the Kaplan-Meier method, in months
    b. The median overall survival (OS) and median progression free survival (PFS) in Arm

B and the observed number of subjects in the group, calculated using the Kaplan-Meier method, in months

3. The Conditional Power (CP) of the trial at the time of the IA based on items 1a. – 1c. and the formula provided for both OS and PFS in Section 5.4.3.1.

5.4.3.1 *Conditional Power Calculation*

The CP will be calculated for each primary endpoint (i.e. OS and PFS) according to the formula (Jenninson and Turnbull [2000] pages 205 to 208) per the metrics calculated above using the formula:

$$CP_k(\theta) = \Phi\left(\frac{Z_k\sqrt{I_k} - z_{1-\alpha/2}\sqrt{I_K} + \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right) + \Phi\left(\frac{-Z_k\sqrt{I_k} - z_{1-\alpha/2}\sqrt{I_K} - \theta(I_K - I_k)}{\sqrt{I_K - I_k}}\right)$$

where:

- θ = the observed treatment effect at the time of the interim analysis [log(HR) using OS and PFS data at the time of the IA] and:
- k = an interim stage at which the conditional power is computed
- K = the stage at which the study is terminated and the final test is computed Z_k = the logrank test statistic calculated from the observed data that has been collected up to stage k, $\frac{S_k}{\sqrt{\hat{I}_k}}$, where S_k is the logrank score statistic computed from the observed data and $\hat{I}_k$ is the estimated information at stage k
- I_k = the information level at stage k; $I_k = [E_k * P_c * (1-P_c)$; where E_k is the number of events at stage k and P_c is the proportion of subjects assigned to the control group (Arm B)]
- I_K = the information level at the end of the study; $I_K = [E * P_c * (1-P_c)$; where E is the total number of events and P_c is the proportion of subjects assigned to the control group (Arm B)]
- $Z_{1-\alpha}$ = the standard normal value for the test with at type I error rate of α

The resulting Conditional Power (CP) from the two primary endpoints will be reported to the DSMB and used to determine whether the sample size needs to be increased or remains unchanged.

5.4.3.2 *Procedure for Re-estimation of the Sample Size*

The re-estimation of the sample size plan will be performed while preserving alpha according to Mehta and Pocock (2010).

The sample size for the study will be adjusted only if the Interim Analysis CP for at least one of the primary endpoints OS or PFS is less than 90% and greater than 33% (i.e., if CP for at least one of the primary endpoints is in the promising zone). In the event that both the CP from OS and PFS are in the promising zone, the lower CP will be used for adjustment of the sample size. The adjustment would be an increase in the target number of events (i.e., deaths or PD) needed in the study in order to bring the CP to at least 90% up to a maximum increase of 436 subjects (218 per group), using the observed effect size at the time of the interim analysis. If the sample size is increased to the maximum of 436 subjects, it is expected that the trial duration will be increased by 2.5 years.

If and only if the interim analysis CP is less than 90% and greater than 33% then the sample size will be re-estimated, up to 436 subjects. The sample size calculation will be performed under the same assumptions as the initial sample size calculation, with the exception of inserting the observed 1) hazard ratio of OS and median overall survival and 2) hazard ratio of PFS and median progression free survival in the treatment and control groups at the time of the interim analysis.

The sample size will be maintained at the original sample size if the CP is greater than or equal to 90% or if the CP is less than or equal 33%. If a sample size re-estimate is required, the re-estimated sample size will be reported to the DSMB. Regardless of the size of the CP at IA, the original sample size will not be reduced nor will the trial be stopped early for efficacy.

The DSMB will make recommendations to sponsor on the continuation/modification/ termination based on the interim safety and conditional power results.

5.4.4 Preservation of Type I Error Rate

Per the Mehta and Pocock (2010) paper, if one increases the sample size only when interim results are promising, a conventional hypothesis test can be performed without inflating the type-1 error. By following the procedure of Mehta and Pocock (2010), if the conditional power at the interim analysis is greater than 33%, performing an unblinded interim analysis and sample size re-estimation will not have an affect on alpha and the overall type I error at the end of the study will be preserved. The cutoff value of 33% chosen based on the guidance from Mehta and Pocock (2010) with a maximum allowed re-estimation of two times the original sample size, an interim look when 60% of expected events occur, and a targeted conditional power of 90%.

5.4.5 Firewall for Protection Against Bias

The procedures for this IA will be based on a standard operating procedure (SOP) that has a well-established a firewall to protect the integrity of the trial. The IA will be performed by an independent

statistician, who is not otherwise associated with the conduct of this trial. Since the study is an open label study after the blinded randomized assignment to study arm, SynCore and the CRO will be provided all results of the interim analysis and the decision of the DSMB to a) stop the trial due to safety, b) continue the trial with the original sample size, without p-value adjustment of the final analyses, c) continue the trial with a re-estimated sample size.

In order to prevent unauthorized persons from accessing the unblinded interim analysis materials and results, a restricted, secure web-based system will be created. This system will centrally store the interim analysis results and reports, DSMB agenda and meeting minutes, and any other relevant DSMB materials. Team members granted access to the restricted system based on their role in the study. No person who is involved in the conduct of the study will be granted access to the restricted system.

To ensure that no bias will be introduced into the conduct of the trial, SynCore, the CRO, nor any other entity associated with the conduct of the trial will perform any unblinded analyses until the trial is completed and the database is locked.

5.5 Subgroup Analysis

The following subgroups will be analyzed for the primary efficacy data of the study:

- Age
- Gender
- Disease stage (Metastatic vs Locally advanced)
- ECOG performance status (0 vs 1)
- Region (United States, Taiwan, Korea, France, Russia, Hungary, Israel)

5.6 Covariates

In the efficacy analysis, the pre-specified stratification factors stated in Section 3.2.2 will be included in the model.

5.7 Multi-center Studies and Pooling of Centers

There are expected to be up to 100 study sites in this study. Due to the large number of study sites and the small numbers of subjects per site, the analysis of efficacy endpoints will not include adjustments for specific study site. However, subgroup analysis by Region (United States, Taiwan, Korea, France, Russia, Hungary and Israel) will be peformed.

6. STATISTICAL ANALYSIS METHODOLOGY

All data collected for this study will be presented in summary tables, listings, and figures (TLFs) as indicated in Appendix 1 of this SAP. Shells for TLFs with enough detail for programming will be provided as a guide to develop the programming SAS codes. These shells will be in sufficient detail to simulate the actual TLFs when they are created from the locked database.

Tabulations for continuous data will use a standard set of summary statistics: number of observations available (n), mean, standard deviation (SD), median, and range (minimum, maximum).

Categorical or dichotomous data will be tabulated using counts and percentages. The numerator and denominator for each percentage calculation will be specified in the footnotes of table shells.

Data listings will present all information recorded in eCRFs and any derived variable(s) included in the analysis datasets for all subjects and visits.

6.1 Study Subjects

6.1.1 Subject Disposition

The final study disposition of each subject will be captured in the eCRF. For those subjects who do not complete the study as planned, all potential reasons for discontinuation will be provided, with one indicated as primary.

The following categories will be used in the summaries as the number of subjects by treatment arm (with the excpetion of Screened) for all centers combined and for each center separately.

- Screened
- Randomized (Intent-to-Treat Population)
- Randomized and Discontinued before receiving study drug
    - Reason for Discontinuation before receiving study drug
- Randomized and received at least a partial first dose of study drug (Safety Population)
- Discontinued after receving study drug
    - Reason for Discontinuation after receving study drug
- Per Protocol Population
- Completed Study, defined as a subject who completes at least the 48-week Follow-Up period after end (or discontinuation) of treatment, regardless of tumor response

A listing of subject disposition will be prepared, inclusive of dates of last dose and last contact, and any investigator comments regarding reason for discontinuation. A summary table will tabulate overall disposition of the subjects by the categories above. An additional summary table will summarize

number of screen failure subjects and reasons for screen failure. A CONsolidated Standards Of Reporting Trials (CONSORT) figure will summarize subject disposition from screening to completion.

6.1.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedure defined in the protocol.

The following categories will be used to group protocol deviations

1. Eligibility/Enrollment
2. Out of Visit Window
3. Protocol Procedure/Assessment
4. Investigational Product Administration
5. Other

The following are categorical reasons used to document why a protocol deviation occurred:

1. Subject illness
2. Subject unable to comply
3. Subject refusal
4. Clinical error
5. Pharmacy error
6. Laboratory error
7. Investigator/staff decision
8. Sponsor decision
9. Other

A subset of the protocol deviations can be identified as a major protocol deviation as described below:

> Major Protocol Deviation: A Major protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Major protocol deviations include but are not limited to:

- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received an excluded concomitant medication.
- A research subject does not meet the protocol's eligibility criteria but was enrolled without prior approval from the sponsor.

- Failure to obtain informed consent prior to initiation of study-related procedures
- Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes.
- Changing the protocol without prior sponsor and IRB approval.
- Multiple minor violations of the same nature after multiple warnings.

Upon soft lock of database, all documented protocol deviations in the study will be reviewed to identify all important protocol deviations by a data review team including representatives from clinical operations, medical, data management, and statistics, and sent to the sponsor for approval. Final decisions will be documented and databased.

A summary table of post-randomization protocol deviations will be presented by treatment arm and overall. The number and proportion of subjects with protocol deviations (major/minordeviations) will be tabulated by protocol deviation category.

6.1.3 **Demographics**

Descriptive summaries of the Safety Population will be prepared for the demographic and baseline (Screening) parameters listed below. Categorical variables will be described with counts and percentages and continuous variables with mean and standard deviation (SD). These variables will also be summarized for the ITT population if it differs from the safety population by more than 10% in overall sample size).

- Age (years)
- Age Group (<65 vs. ≥65)
- Gender
- Race/ethnicity
- Disease State (Metastatic vs. Locally Advanced)
- ECOG Performance Status (0 vs. 1)
- Country
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

6.1.4 **Medical and Surgical History**

At the Screening visit, the general medical and surgical procedures history will be recorded on the eCRF, Medical History data will be summarized in a table by MedDRA version 23.0 System Organ class (SOC) and Preferred Term (PT). Data listings for medical history and surgical history will be provided.

6.1.5 Concomitant Medications

All prior and concomitant medications, interventions and procedures will be tabulated. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization Drug (WHODrug) classifications version March 1 2020.

A by-subject listing comprehensive of prior and concomitant medications will be generated, inclusive of verbatim and coded terms, doses and routes, and start and stop dates. Prior medications will be flagged. Prior and concomitant status with respect to study drug treatment will be determined based on imputed dates. Prior medications used within 30 days of Screening will be provided in a separate listing.

6.2 Efficacy Analysis

6.2.1 Primary Efficacy Analysis

The primary efficacy endpoints for the study are:

1. Overall Survival
2. Progression Free Survival

As discussed in Section 5.2, to maintain the trial-wise Type I error rate at 0.05, a hierarchical test procedure with fixed sequence will be used. PFS will only be compared if the primary analysis of OS rejects the null hypothesis.

6.2.1.1 *Overall Survival*

Overall survival (OS) is defined as the time from randomization to death from any cause or last day known to be alive. OS will be defined in months, where:

$$Overall\ Survival\ =\ (date\ of\ death\ or\ last\ day\ known\ to\ be\ alive - date\ of\ randomization\ +\ 1)/30$$

The below dates will be used in order to determine the date of death or last day known to be alive used for Overall Survival calculation:

Table 6-1: Date of Death or Censoring for Overall Survival Situation

Order	Situation	Date of Death or Censoring	Outcome
1	Subject died	Date of Death	Dead
2	Subject known to be alive in the survival follow-up	Date of last day known to be alive	Censored
3	Subject completed the study	Date of study completion	Censored
4	Subject withdrew from the study or was lost to follow-up after randomization	Date of withdraw from the study or lost to follow-up	Censored
5	Subject did not withdrawal nor lost to follow-up and is still in the study	Date of last visit	Censored

6.2.1.2 *Progression Free Survival*

Progression Free Survival (PFS) is defined as the time from randomization to either first observation of progressive disease or occurrence of death. To assess progression, it is necessary to estimate the overall tumour burden at baseline. The tumor imaging as the Screening Visit will be used as the baseline measurement. Tumor imaging will be completed every 8 weeks irrespective of the timing of the treatment cycle. When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters in millimeters.

At baseline, all other non-target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurement of these lesions will be as follows:

Response	Definition
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

At the post-baseline tumor imaging assessments, the sum of diameters will be measured. Progressive disease will be considered at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum of diameters or any other post-baseline calculated sum of diameters before a respective imaging visit). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters. Additionally, the appearance of one or more new lesions compared to the baseline assessment is also considered progression at any post-baseline visit.

Following any post-baseline imaging, the investigator will determine if the disease is progressive based on the above criteria and record the response in the eCRF.

The date of progression free survival will be considered the date of first observation of progressive disease or the last known day to be alive, whichever is first. For the calculation of the end of progression free survival, in months, the following formula will be used:

$$Progression\ Free\ Survival = (date\ of\ first\ observation\ of\ progressive\ diease\ \ or\ last\ day\ known$$

$$to\ be\ alive - date\ of\ randomization + 1) / 30$$

The below dates will be used in order to determine the first observation of progressive diease or last day known to be alive used for Progression Free Survival calculation:

Table 6-2: Date of Death or Censoring for Progression Free Survival Situation

Order	Situation	Date of Progression or Censoring	Outcome
1	Incomplete or no baseline tumor assessments	Randomization	Censored
2	Subjects died or disease progressed	Date of Death or Date of first observation of progressive disease, whichever is first	Progressed
3	Subjects completed the study with no disease progression	Date of study completion	Censored
4	Subjects did not withdrawal nor lost to follow-up and are still in the study with no disease progression	Date of last visit	Censored
5	Subjects who have two or more consecutive missing tumor assessments before a PFS event	Date of last visit prior to the PFS event	Censored
6	Subjects who receive a new anti-cancer therapy with no documented progression	Date of last visit prior to the initiation of new anti-cancer therapy	Censored
7A	Treatment discontinuation for toxicity or other reason	Date of last progression with no documented progression	Censored
7B	Treatment discontinuation for toxicity or other reason	Date of documented progression with protocol specified continued follow-up in all treatment arms	Progressed

6.2.1.3 *Null Hypothesis of the Primary Effiacy Analysis*

For PFS, the null hypothesis is that there is no difference in PFS between the treatment groups Arm A and Arm B. The alternative hypothesis is that there is a difference in PFS between treatment groups Arm A and Arm B.

For OS, the null hypothesis is that there is no difference in overall survival between the treatment groups Arm A and Arm B. The alternative hypothesis is that there is a difference in overall survival between treatment groups Arm A and Arm B.

6.2.1.4 *Primary Efficacy Analysis*

Primary efficacy endpoints will be compared between the treatment arms using stratified log-rank test with the factors ECOG status (0 vs. 1) and disease stage (Metastatic vs. Locally Advanced)

included as stratification. The differences between treatment arms, its 95% Confidence Interval (CI), and p-value will be reported.

In addition, the Kaplan-Meier method will also be used to depict the median, the 1st quartile, and 3rd quartile time to PD or death from any cause for the treatment arms. A Kaplan-Meier plot will present the non-parametric function by treatment arm.

The Primary Efficacy Analyses will be tested on the Intent-to-Treat Population. In addition, it will be carried out on the Per Protocol Population and will be considered supportive analysis.

6.2.2 Secondary Efficacy Analyses

To maintain the trial-wise Type I error rate at 0.05, a closed test procedure will be used for the secondary endpoints. The order of the endpoints will be as follows:

1. Percentage of subjects with Objective Response (OR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1)
2. Duration of Response (DR)
3. Percentage of subjects with disease control according to RECIST v.1.1
4. Serum Carbohydrate Antigen 19-9 (CA 19-9) response rate

Any Secondary Efficacy Analyses that are carried out will be tested on the Intent-to-Treat Population. In addition, they will be carried out on the Per Protocol Population and will be considered supportive analyses.

6.2.2.1 *Objective Response*

The percentage of subjects with Objective Response (OR) during the course of the study according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1) will be summarized.

To assess objective response, it is necessary to estimate the overall tumour burden at baseline. The tumor imaging as the Screening Visit will be used as the baseline measurement. Tumor imaging will be completed every 8 weeks irrespective of the timing of the treatment cycle. When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a

maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters in millimeters.

At any post-baseline imaging assessment, the investigator will determine and record in the eCRF whether there is a complete response (CR) or partial response (PR) where:

- Complete Response = Disappearance of all target lesions
- Partial Response = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters

If a subject has a CR or PR at any visit during treatment or follow-up, they will be considered as having an objective response.

The number and frequency of subjects who have an objective response by treatment arm will be presented. To test the difference in proportions between the two groups, a logistic regression model will be used. The model will include factors ECOG status (0 vs. 1) and disease stage (Metastatic vs. Locally Advanced). The p-value for the treatment arm variable will be reported.

6.2.2.2 ***Duration of Response***

Duration of Response (DR) is defined as the time from the first documentation of objective tumor response to objective tumor progression or death due to any cause. The date of objective response and the date of progression are defined as in Section 6.2.2.1 and 6.2.1.1, respectively. The earliest date with CR or PR will be considered the date of objective response. The date of tumor progression will be considered the earliest date that PD is objectively documented after the objective response date, taking as reference for PD the smallest measurements recorded since the treatment started. The duration of response, in months, will be calculated as:

$$Duration\ of\ Response = (date\ of\ tumor\ progression\ or\ death - date\ of\ first\ objective\ response\ (CR\ or\ PR) + 1) / 30$$

Date of tumor progression or death will be determined following Table 6-2.

This endpoint will only be evaluated in subjects with objective response of CR or PR. The analysis of duration of responses will only be used as a descriptive analysis.

In addition, the Kaplan-Meier method will also be used to depict the median, the 1st quartile, and 3rd quartile Duration of Response for the treatment arms.

6.2.2.3 ***Disease Control***

Percentage of subjects with disease control will be summarized. Disease control is based on assessment of complete response (CR) or partial response (PR) or stable disease (SD) according to RECIST v.1.1.

CR and PR are defined as in Section 6.2.2.1. Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. If a subject is classified as CR, PR, or SD at their last imaging visit, they will be considered to have disease control. If a subject died while on study, they will be classified as failed to have disease control irregardless of previous imaging assessments.

The number and frequency of subjects who have a disease control by treatment arm will be presented. To test the difference in proportions between the two groups, a logistic regression model will be used. The model will include factors ECOG status (0 vs. 1) and disease stage (Metastatic vs. Locally Advanced). The p-value for the treatment arm variable will be reported.

6.2.2.4 *Serum Carbohydrate Antigen 19-9 (CA 19-9) response rate*

Serum Carbohydrte Antigen 19.9 (CA 19-9) will be collected as part of the laboratory assessments at Screening, on week 8 of treatment cycles, and at Follow-up Visit 1. The Screening assessment will be considered the baseline assessment. Responders are defined as subjects with a reduction in Serum Carbohydrate Antigen 19.9 (CA 19-9) levels by least 50% from baseline to the end of cycle 1 (or end of full treatment course). If a subject died while on study, they will be classified as a failure, irregardless of previous assessments.

The number and frequency of subjects who have a disease control by treatment arm will be presented. To test the difference in proportions between the two groups, a logistic regression model will be used. The model will include factors ECOG status (0 vs. 1) and disease stage (Metastatic vs. Locally Advanced). The p-value for the treatment arm variable will be reported.

6.2.3 Exploratory Analyses

1. Change from Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score

2. Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score

6.2.3.1 *EORTC-QLQ-C30 Summary Score*

Change from Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Summary Score will be performed. The assessment at the Screening visit will be considered the baseline assessment.

EORTC QLQ-C30 score will be evaluated for the following domains:

- Global health QoL:
  - ✓ (items 29 and 30)

- Functional scales including:
  - ✓ Physical (items 1 to 5),
  - ✓ Role (items 6 and 7),
  - ✓ Cognitive (items 20 and 25),
  - ✓ Emotional (items 21 to 24) and,
  - ✓ Social (items 26 and 27).

- Symptom scales including:
  - ✓ Fatigue (items 10, 12, and 18),
  - ✓ Pain (items 9 and 19) and,
  - ✓ Nausea/vomiting (items 14 and 15).

- Side effect scales and overall side effect bother scales including:
  - ✓ Dyspnoea (item 8),
  - ✓ Appetite loss (item 13),
  - ✓ Insomnia (item 11) and,
  - ✓ Constipation/diarrhea (items 16 and 17).

All scales in the summary score consist of questions that use a 4- point scale (1 'Not at All' to 4 'Very Much').

EORTC-QLQ-C30 change from baseline for each category will be calculated at Follow-up Visit 1 and will be summarized by treatmentgroup (n, mean, standard deviation, median, minimum and maximum).

To test for the difference in change from baseline between treatment groups, the following methods will be used, as appropriate:

- If the normality assumption is met, Analysis of Covariance (ANCOVA). The model will consist of the Follow-up Visit 1 value as the dependent variable and with the baseline value, time, time x treatment interaction, and the covariates from Section 5.6 in the model, as necessary.
- If the Normality assumption is not met, a rank–ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

The p-values for the appropriate analysis will be presented.

6.2.3.2 ***EORTC-QLQ-PAN26***

Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Scorewill be performed. The assessment at the Screening visit will be considered the baseline assessment.

QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment side effects and emotional issues specific to pancreatic cancer (PC). Questions include on altered bowel habits, pain, dietary changes, disease and Tx-related symptoms and issues related to the emotional and social well-being of participants with PC. All 26 Qs are answered on 4-point Likert scale ranging from '1=not at all' to 4='very much' and subsequently transformed into scales that range from 0-100; higher scores= greater degree of symptoms or treatment side effects and emotional issues.

PAN26 score will be evaluated for 7 domain scores as below:

- Pancreatic pain (item 31, 33, 34 and 35)
- Digestive (item 36 and 37),
- Altered bowel habit (item 46 and 47),
- Hepatic (item 44 and 45),
- Body image (item 48 and 49),
- Health care satisfaction (item 53 and 54) and,
- Sexuality (item 55 and 56).

The mean of the each domain will be calculated and will be considered the EORTC-QLQ-PAN26 score for a given visit. EORTC-QLQ-PAN26 change from baseline for each domain will be calculated at Follow-up Visit 1 and will be summarized by treatmentgroup (n, mean, standard deviation, median, minimum and maximum).

To test for the difference in change from baseline between treatment groups, the following methods will be used, as appropriate:

- If the normality assumption is met, Analysis of Covariance (ANCOVA). The model will consist of the Follow-up Visit 1 value as the dependent variable and with the baseline value, time, time x treatment interaction, and the covariates from Section 5.6 in the model, as necessary.
- If the Normality assumption is not met, a rank–ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.

The p-values for the appropriate analysis will be presented.

6.3 Safety Analysis

6.3.1 Exposure

Summary statistics will be presented for the time on treatment in months by study arm, where the time on treatment will be calculated as:

Time on Treatment = (Date of Last Dose – Date of First Dose) / 30

The time on treatment will be summarized by treatment arm for the ITT Population, the Per Protocol Population, and the Safety Population.

6.3.2 Adverse Events

All adverse events will be coded using version 23.0 of MedDRA, which will be noted in the CSR.

A treatment-emergent adverse experience (TEAE) is defined as any event that only occurred after the first dose of the study drug (Day 1 of the first cycle for Arm A and Day 4 of the first cycle for Arm B) or that existed before drug administration but increased in severity or treatment attribution.

The duration of an AE will be calculated as:

Duration = (AE End Date – AE Onset Date) + 1

The incidence of TEAEs and treatment emergent serious adverse events (SAEs) will be summarized.

An overall summary of TEAEs will include:

- Incidence of subjects with one or more TEAE
- Incidence of TEAEs by highest relationship
- Incidence of TEAEs by highest severity
- Incidence of TEAEs by action taken
- Incidence of TEAEs by outcome
- Incidence of treatment-emergent SAEs

The incidence of TEAEs will be presented by the following separately:

- System Organ Classification and Preferred Term
- Preferred Term in descending order of frequency of events overall
- System Organ Classification and Preferred Term by maximum intensity
- System Organ Classification and Preferred Term by highest relationship,

- Treatment-related TEAE by System Organ Classification and Preferred Term by highest relationship (possibly, probably, definitely)
- TEAE leading to discontinuation by System Organ Classification and Preferred Term

In addition, separate summaries of TEAEs will be prepared with subjects categorized by System Organ Classification and Preferred Term and by sex, age, and race.

The incidence of treatment-emergent serious adverse events (SAEs) will be presented by system organ classification and preferred terms, by treatment-related status (possibly, probably, certainly), and for those that are fatal.

Adverse events will be listed for all subjects, including verbatim and coded terms.

6.3.3 Clinical Laboratory Tests

Serum chemistry laboratory tests will be collected at Screening, Visits 1G, 2G, and 8 of the First Cycle Treatment Phase, Visit 8 of Subsequent Cycle Treatment Phases, and Follow-up Visit 1 after the last treatment cycle. The following serum chemistry parameters will be used for safety analysis:

- Urea
- Serum Creatinine
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Glucose
- Bilirubin
- Albumin
- Alanine Aminotransferase (ALT)
- Aspartate Aminotransferase (AST)
- Alkaline Phosphatase (ALP)
- Total protein

Hematology laboratory tests will be collected at Screening, every non-rest visit during the Treatment Phases, and Follow-up Visit 1 after the last treatment cycle. The following hematology parameters will be used for safety analysis:

- Hemoglobin
- Hematocrit (HCT)
- Mean Corpuscular Volume (MCV)

- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- Red Blood Cell (RBC) count
- Platelets count
- White Blood Cell (WBC) count
- WBC Differential
- Differential Leukocyte count
- Absolute Neutrophil count

Coagulation laboratory tests will be collected at Screening, Visits 1G, 2G, 3G, 5G, 6G, 7G, and 8 of treatment phases for each cycle, and Follow-up Visit 1 after the last treatment cycle. The following coagulation parameters will be used for safety analysis:

- International Normalized Ratio (INR)
- Prothrombin Time (PT)
- Activated partial thromboplastin time (APTT)
- Total Fibrinogen

Urinalysis laboratory tests will be collected at Screening, Visit 8 of treatment phase for each cycle, and Follow-up Visit 1 after the last treatment cycle. The following urinalysis parameters will be used for safety analysis:

- pH
- Appearance
- Color
- Specific Gravity
- Viscosity
- Turbidity
- Ketones
- Bilirubin
- Blood
- Glucose
- Protein
- Nitrites
- Urobilinogen
- Leukocyte Esterases
- Microscopic Exam:

- Bacteria
- Cast
- Crystals
- Epithelial cells
- RBC
- WBC

Baseline for each lab parameter will be considered the last assessment before the dose administration on Study Day 1 (date of First Cycle First Dose as described in Section 4.5.1) for serum chemistry, hematology, and coagulation and as the Screening assessment for urinalysis.

For continuous endpoints, summary statistics for the outcome at each available week's assessment and its change from baseline will be tabulated separately for chemistry, hematology, coagulation, and urinalysis parameters. Additionally, number and propotion of subjects with investigator-determined abnormal lab results will be tabulated as a shift table by treatment arm with baseline vs. respective week presented for each parameter. Number and proportion of subjects with clinically significant abnormal results will also be presented by week and by treatment arm in a table. For summary tables, the visits will be presented as Screening, "Treatment Phase X, Visit Y," and Follow-Up Phase. The Follow-up Phase will present the Follow-up Visit 1 for all subjects, regardless of the number of treatment cycles completed.

Clinical laboratory results will be listed for all subjects, inclusive of flags for whether or not the value is outside laboratory normal range or considered significant by the Investigator. Normal ranges will be noted in the listing. Values outside laboratory normal ranges as well as those considered clinically significant by the Investigator will be flagged as L (low) and H (high).

Pregnancy Tests and Tumor Marker CA 19-9 collected throughout the study will also be presented in listings.

6.3.4 **Vital Signs**

Vital Signs are collected at Screening, all Treatment Phase visits for each cycle, and Follow-up Visit 1 after the last treatment phase. The following vital signs parameters will be collected:

- Systolic Blood Pressure (SBP)
- Diastolic Blood Pressure (DBP)
- Heart Rate
- Body Temperature
- Weight

Summary statistics for the parameters at each available week's assessment and its change from baseline will be tabulated SBP, DBP, and Heart Rate. Additionally, number and propotion of subjects with investigator-determined abnormal vital sign results will be tabulated as a shift table by treatment arm with baseline vs. respective visit presented for each parameter. Number and proportion of subjects with clinically significant abnormal results will also be presented by week and by treatment arm in a table. For summary tables, the visits will be presented as Screening, "Treatment Phase X, Visit Y," and Follow-Up Phase. The Follow-up Phase will present the Follow-up Visit 1 for all subjects, regardless of the number of treatment cycles completed.

All vital sign results will be listed for all subjects, inclusive of flags for whether or not the value is outside normal range or considered significant by the Investigator. Normal ranges will be noted in the listing. Values outside laboratory normal ranges as well as those considered clinically significant by the Investigator will be flagged as L (low) and H (high).

6.3.5 **12-lead Electrocardiogram**

Electrocardiograms will be performed at Screening and every 8 weeks regardless of treatment cycle. Parameters to be summarized include:

- Heart Ratet (HR)
- PR Interval
- RR Interval
- QRS
- QT
- QTc with the Bazett correction ($QTcB= QT/(RR)^{1/2}$)
- QTc with the Fridericia correction ($QTcF = QT/(RR)^{1/3}$)

All triplicate results will be averaged for summary and analysis purposes.

ECG results will be summarized by treatment arm and week. Descriptive statistics will include mean, standard deviation, median, minimum, and maximum. Continuous ECG parameters will be summarized as change from Baseline (Screening Assessment). For the summary of change statistics, the Baseline mean and standard deviation will be provided for the subset of subjects with available data for the change summary. Clinical interpretations will also be summarized by visit and treatment arm. For summary tables, the visits will be presented as Screening, "Treatment Phase X, Visit 8," and Follow-Up Phase. The Follow-up Phase will present the Follow-up Visit 1 for all subjects, regardless of the number of treatment cycles completed.

ECG results, including clinical interpretation and a flag for whether or not the value meets criteria for being possibly clinically significant, will be listed for all subjects. Any ECG abnormalities, based on clinical interpretation, will be listed.

6.3.6 Physical Exam

Complete physical examination is to be performed at Screening, Visits 1G, 2G, 3G, 5G, 6G, 7G, and 8 of treatment phases for each cycle, and Follow-up Visit 1 after each treatment cycle. The complete examination will consist of evaluation of the following:

- Skin
- Head
- Eyes
- Ears
- Nose
- Throat
- Neck
- Thyroid
- Lungs
- Heart
- Lymph nodes
- Abdomen
- Extremities

Descriptive statistics will be provided for proportions of subjects with abnormalities on physical examination by treatment arm at each week. Physical examination findings will be listed.

6.4 Pharmacokinetics

A separate SAP will be prepared that describes the methodology to be used in analyzing pharmacokinetic (PK) data.

7. TESTING/QUALITY CONTROL PLAN AND SOFTWARE/SYSTEM

All statistical programs will be written in SAS® version 9.3 or higher [6]. Statistical programs will be tested and reviewed for Quality Control (QC) by a second programmer/biostatistician not involved in the programming as per DP Clinical (CRO)'s standard operating procedure (SOP). In addition, CRO's SOP will be followed to ensure that the information is complete, consistent, and accurately reflects the data stored in Clinical Data Management System (CDMS) database. Further all tables, listings, and figures (TLFs) will undergo a QC process by an independent biostatistician/programmer to ensure that the information is complete, consistent, and accurately reflects the data stored in CDMS.

7.1 Programming Specifications for TLFs

Appendix 1 provides a list of all the TLFs that are planned to be produced.

7.2 Formatting Conventions

The following formatting conventions will be used to output TLFs:

- TLFs are outputted by SAS Output Delivery System (ODS) into Rich Text Files (RTF) format.
- Tables and Listings will include borders around all headings and data cells.
- Output will be in landscape orientation with margins of 1.5 inches on top, and 1 inch for right, left, and bottom.
- The default font to be in tables/listings/figures will be Courier New.
- Preferred and minimum font size:

Portion of Output	Preferred	Minimum
Page Header	10 pt	8 pt
Title	10 pt	8 pt
Column header	10 pt	8 pt
Cells	10 pt	8 pt
Footnote	10 pt	8 pt
Page Footer	10 pt	8 pt

- Data will be centered within columns when the maximum length of the data being displayed is less than or equal to the maximum width of the column heading. When the maximum length of the data being displayed exceeds the maximum width of the column heading, the data will be left-justified.
- Column headings should be in initial capital characters. For numeric variables, include "unit" in the column heading when appropriate.

- In figures, axes will be labeled appropriately.

7.3 Standard Text Conventions

7.3.1 Header

All output (table, listing, or figure) will have the following header:

SynCore Biotechnology Co., Ltd.
Protocol: CT 4006 Page xx of XX
[Output Type]

where [Output Type] is "Interim Analysis," "Clinical Study Report," etc as appropriate. All output will have the date and time (date and time output was generated) and internal page number in the footer. Tables/Listings/Figures should be internally paginated (i.e., page numbers should appear sequentially within each output).

7.3.2 Title

At least three (3) lines, in general, will be reserved for the entire title.

- The first line is for the table/listing/figure number;
- The second line is for the actual title; and
- The third line is reserved for the analysis population descriptor.

All titles will be centered, as shown in the following example:

Table 14.3.1.1
Topline Summary of Safety Events
Safety Population

7.3.3 Footnotes

Unless otherwise specified, footnotes will appear on all pages within the tables and listings as follows:

- Footnotes will be in the format of "Note: followed by 2 spaces, then the footnotes", as shown in the following example:

  Note: SD = Standard Deviation; SEM = Standard Error of the Mean.

- Each line of a complete footnote should end with a period.
- When an abbreviation (e.g. AE, SAE, etc.) appears first time in the whole set of TLFs for a study, a footnote should be provided at least once; and it is up to the

study statistician, to decide whether there is a need to repeat the same footnote for the rest of TLFs.

- A footnote serves as a brief explanation/clarification /definition /concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or relates directly to the displayed content of a table/listing/figure.
- Footnotes will not contain detailed/technical elaboration of, for example, a mathematical/statistical formula, a statistical term/test, or an algorithm for deriving a parameter value, which should be addressed in the text of the SAP.
- All footnotes will be at the lowest line of the page immediately above the footer. There will be one space between the last footnote and the footer.
- For Tables, first footnote will provide source listings and/or analysis datasets names for cross-referencing.

7.3.4 Footer

The following footer should appear at the very bottom of each page of a table, a listing, or a figure generated in SAS in the lower left corner:

Program: PGNAME.sas; Creation Date and Time: MMDDDYYYY HH:MM
Data Cutoff: DDMMMYY:HH:MM:SS – Listing Generated MMM DD, YYYY

where PGNAME = SAS program name.

7.4 Statistical Conventions

7.4.1 Statistics Reported

- Unless otherwise specified, the mean and standard deviation (SD) will be displayed to one more decimal place than the original value, while minimum and maximum will be reported in the format of the original data, e.g.:

  Original: xx
  Mean and SD: xx.x
  Minimum and maximum: xx

- Descriptive statistics in this template include: **Mean, Median, Standard Deviation (SD), Minimum, Maximum, and N**. In addition, 95% CI will be presented when appropriate.

- Unless specified in the actual TLF shells for a study, all percentages will be rounded to 1 decimal place in all tables/listings/figures. Rounding will take place after all calculations have been performed.

- Use of N versus n:

  N = total number of subjects or subjects in the population.

  n = total number of subjects or subjects in the specific category.

7.4.2 SAS Procedure Output

If appropriate, SAS procedure output may be formatted and saved as source for references and will be included in Appendix.

7.4.3 Tables Summarizing Categorical Data

The following specifications apply to tables that summarize categorical data:

- Percent of events should be left blank (including the parentheses) if the number of events is zero.
- If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category will be included, even if n=0 for a given category between the minimum and maximum level for that parameter.
- If the categories are not ordered, then only those categories for which there is at least one subject represented will be included.
- A missing category will be added to any parameter for which information is not available for any subjects.

7.4.4 Subject Data Listings

In general, individual subject data listings should include all subjects with data. However, if a subject data listing includes only subjects who met a certain condition, and there were no subjects who met that condition, then a “message” will appear indicating that no subjects met the condition for inclusion in that listing.

8. REFERENCES

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9. APPENDICES

9.1 Planned Tables, Listings, and Figures

Output Number	Output Name	Study Population
Table 14.1.1.1	Screen Failure Summary	Screened Population
Table 14.1.1.2	Subject Disposition	Screened Population
Table 14.1.2	Protocol Deviations	Safety Population
Table 14.1.3.1	Demographics and Baseline Characteristics	Safety Population
Table 14.1.3.2	Demographics and Baseline Characteristics	ITT Population
Table 14.1.4.1	Medical History	Safety Population
Table 14.1.4.2	Prior Medications	Safety Population
Table 14.1.4.3	Concomitant Medications	Safety Population
Table 14.1.5	Study Drug Exposure	Safety Population
Table 14.2.1.1A	Progression Free Survival by Treatment Arm	ITT Population
Table 14.2.1.1B	Progression Free Survival by Treatment Arm	Per Protocol Population
Table 14.2.1.2A	Overall Survival by Treatment Arm	ITT Population
Table 14.2.1.2B	Overall Survival by Treatment Arm	Per Protocol Population
Table 14.2.2.1A	Objective Response by Treatment Arm	ITT Population
Table 14.2.2.1B	Objective Response by Treatment Arm	Per Protocol Population
Table 14.2.2.2A	Duration of Response by Treatment Arm	ITT Population
Table 14.2.2.2B	Duration of Response by Treatment Arm	Per Protocol Population
Table 14.2.2.3A	Disease Control by Treatment Arm	ITT Population
Table 14.2.2.3B	Disease Control by Treatment Arm	Per Protocol Population
Table 14.2.2.4A	EORTC QLQ-C30 Summary Score Change from Baseline by Treatment Group	ITT Population
Table 14.2.2.4B	EORTC QLQ-C30 Summary Score Change from Baseline by Treatment Group	Per Protocol Population
Table 14.2.2.5A	EORTC QLQ-PAN26 Summary Score Change from Baseline by Treatment Group	ITT Population
Table 14.2.2.5B	EORTC QLQ-PAN26 Summary Score Change from Baseline by Treatment Group	Per Protocol Population
Table 14.2.2.6A	Serum Carbohydrate Response by Treatment Group	ITT Population
Table 14.2.2.6B	Serum Carbohydrate Response by Treatment Group	Per Protocol Population
Table 14.3.1.1	Topline Summary of Treatment Emergent Adverse Events	Safety Population

Table 14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.1.3	Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency	Safety Population
Table 14.3.1.4	Treatment Emergent Adverse Events by Maximum Severity	Safety Population
Table 14.3.1.5	Treatment Emergent Adverse Events by Highest Relationship to Study Drug	Safety Population
Table 14.3.1.6	Treatment Emergent Treatment Related Adverse Events by Highest Relationship to Study Drug	Safety Population
Table 14.3.1.7	Treatment Emergent Adverse Events Leading to Discontinuation	Safety Population
Table 14.3.1.8.1	Treatment Emergent Adverse Events by XX Subgroup	Safety Population
Table 14.3.1.8.2	Treatment Emergent Adverse Events by XX Subgroup	Safety Population
Table 14.3.1.8.3	Treatment Emergent Adverse Events by XX Subgroup	Safety Population
Table 14.3.2.1	Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2	Treatment Emergent Treatment Related Serious Adverse Events by Highest Relationship to Study Drug	Safety Population
Table 14.3.3	Treatment Emergent Fatal Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.4.1.1	Summary of Vital Signs	Safety Population
Table 14.3.4.1.2	Abnormal Vital Signs Shift Table	Safety Population
Table 14.3.4.1.3	Number and Proportion with Clinically Significant Abnormal Vital Signs Results	Safety Population
Table 14.3.4.2.1	Summary of Hematology Laboratory Results	Safety Population
Table 14.3.4.2.2	Abnormal Hematology Shift Table	Safety Population
Table 14.3.4.2.3	Number and Proportion with Clinically Significant Abnormal Hematology Results	Safety Population
Table 14.3.4.3.1	Summary of Chemistry Laboratory Results	Safety Population
Table 14.3.4.3.2	Abnormal Chemistry Shift Table	Safety Population
Table 14.3.4.3.3	Number and Proportion with Clinically Significant Abnormal Chemistry Results	Safety Population
Table 14.3.4.4.1	Summary of Coagulation Laboratory Results	Safety Population
Table 14.3.4.4.2	Abnormal Coagulation Shift Table	Safety Population
Table 14.3.4.4.3	Number and Proportion with Clinically Significant Abnormal Coagulation Results	Safety Population
Table 14.3.4.5.1	Summary of Urinalysis Laboratory Results	Safety Population
Table 14.3.4.5.2	Abnormal Urinalysis Shift Table	Safety Population
Table 14.3.4.5.3	Number and Proportion with Clinically Significant Abnormal Urinalysis Results	Safety Population
Table 14.3.4.6.1	Summary of 12-Lead Electrocardiogram Parameters	Safety Population
Table 14.3.4.6.2	Clinical Interpretation and Categorical Results of 12-Lead Electrocardiogram	Safety Population

Figure 14.1.1.2.1	Subject Disposition	Screened Population
Figure 14.2.1.1.1	Overall Survival by Treatment Arm	ITT Population
Figure 14.2.1.2.1	Overall Survival by Treatment Arm	Per Protocol Population
Figure 14.2.2.1.1	Progression Free Survival by Treatment Arm	ITT Population
Figure 14.2.2.2.1	Progression Free Survival by Treatment Arm	Per Protocol Population
Figure 14.2.4.1.1	Duration of Response by Treatment Arm	ITT Population
Figure 14.2.4.2.1	Duration of Response by Treatment Arm	Per Protocol Population

Listing 16.1.7	Randomization Scheme	All Enrolled
Listing 16.2.1.1	Subject Eligibility	All Enrolled
Listing 16.2.1.2	Subject Disposition	All Enrolled
Listing 16.2.1.3	Identification of Analysis Sets	All Enrolled
Listing 16.2.2	Protocol Deviations	All Enrolled
Listing 16.2.4.1	Demographics	All Enrolled
Listing 16.2.4.2.1	Medical History	All Enrolled
Listing 16.2.4.2.2	Surgical History	All Enrolled
Listing 16.2.4.2.3	Disease History	All Enrolled
Listing 16.2.4.3	Prior and Concomitant Medications	All Enrolled
Listing 16.2.5	Dose Administration	All Enrolled
Listing 16.2.6.1	Tumor Imaging	All Enrolled
Listing 16.2.6.2	RECIST 1.1 Assessments	All Enrolled
Listing 16.2.6.3	Carbohydrate Antigen 19-9	All Enrolled
Listing 16.2.6.4.1	EORTC QLQ-C30	All Enrolled
Listing 16.2.6.4.2	EORTC QLQ-PAN26	All Enrolled
Listing 16.2.6.5	ECOG Performance Status	All Enrolled
Listing 16.2.6.6	Derived Time-to-Event Efficacy Endpoints	All Enrolled
Listing 16.2.7.1	Adverse Events	All Enrolled
Listing 16.2.7.2	Serious Adverse Events	All Enrolled
Listing 16.2.8.1	Hematology Laboratory	All Enrolled
Listing 16.2.8.2	Chemistry Laboratory	All Enrolled
Listing 16.2.8.3	Coagulation Laboratory	All Enrolled
Listing 16.2.8.4	Urinalysis Laboratory	All Enrolled
Listing 16.2.8.5	Pregnancy Test	All Enrolled
Listing 16.2.9	Vital Signs	All Enrolled

Listing 16.2.10	12-Lead Electrocardiogram	All Enrolled
Listing 16.2.11	Physical Examination	All Enrolled
Listing 16.2.X	Pharmacokinetics (Not Applicable to This SAP)	All Enrolled

9.2 Rationale for changing PFS from secondary endpoint to primary endpoint

Based on a systematic electronic search using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, Fausto P. et al.(1) and Tsuyoshi Hamada et al.(2) have identified 30 randomized controlled trials from 2002 to 2013 and 50 randomized controlled phase II and III trials from 1995 to 2015 in the first-line chemotherapy for patients with advanced pancreatic cancer(PC), respectively. Through a correlation approach to evaluate potential surrogate end-points, PFS, for OS, they found PFS was strongly correlated with OS (correlation coefficient were 0.75 and 0.76 respectively). Weighted linear regression models revealed the greatest determinant coefficient of 0.78 and 0.84 between the hazard ratio (HR) of the experimental arms compared with the control arms of PFS and that of OS. Both of the analytical results implied that PFS can serve as the most suitable surrogate end-point for OS, facilitating early study completion and cost reduction.

Thomas et. al. (3) also mentioned that among all patients receiving first-line chemotherapy for MPC, 49% went on to receive second-line therapy and 19% received third-line therapy; the trend is showing more and more pancreatic cancer patients were given sequential treatments than before. Furthermore, in NCCN guidelines on metastatic pancreatic cancer (4), a wide variety of first and second-line treatments are recommended. Although there is no recommendation for third-line treatments, first and second-line treatments could be selected according to patient's performance status (PS). Both increasing acceptance of physicians to continue treatments and more PC combination treatments available have largely impacted the OS of MPC patients.

As Fausto P. et al. pointed out that an ideal surrogate endpoint (e.g.PFS) would correlate with the true endpoint (OS), and should totally capture the actual treatment effect on the true endpoint. Based on the evidence mentioned above, we change PFS from secondary endpoint to primary endpoint.

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