SynCoreBio

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

Protocol Number:	CT 4006
Investigational Product:	EndoTAG-1 (paclitaxel in cationic liposomes)
Development Phase:	Phase 3
Version/Date:	Version 4.2 /28-Jan-2021
Sponsor:	SynCore Biotechnology Co., Ltd. 4F, No.69, DongXing Rd., XinYi Dist., Taipei City 110, Taiwan Tel:+886-2-2760-3688 Fax: +886-2-2763-9287
Global Coordinating Investigator:	Li-Tzong Chen, M.D., Ph.D. National Institute of Cancer Research, National Health Research Institutes Department of Internal Medicine, National Cheng Kung University Hospital Tainan, Taiwan, R.O.C

Confidentiality Statement

PROTOCOL APPROVAL PAGE

Protocol Number:	**CT 4006**
Version:	**4.2**
Date:	**28-Jan-2021**

Protocol 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

PROTOCOL APPROVAL FOR USE

Muh-Hwan Su, PhD
General Manager
SynCore Biotechnology Co., Ltd.

Signature _____ Date _____

Lin Jia, MS;
Statistician
Amarex Clinical Research, LLC

Signature _____ Date _____

Victoria Martin, MS;
Medical Writer
Amarex Clinical Research, LLC

Signature _____ Date _____

Albert Lin
Head of Clinical Quality Department
SynCore Biotechnology Co., Ltd.

Signature _____ Date _____

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	**CT 4006**
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Protocol 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

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by SynCore Biotechnology. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please retain the original for your study files.

List of Changes from Previous Version

Page no.	Protocol v.4.1 08 Sep 2020	Protocol v.4.2 28-Jan-2021	Note
Protocol Synopsis			
17, 46	**Objectives:** The objective of the study is to assess the safety, efficacy and quality of life 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.	**Objectives:** The objective of the study is to assess the safety and efficacy ~~and quality of life~~ 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.	Remove quality of life from study objective
17, 46	Efficacy Objectives • Assessment of survival (progression-free survival [PFS], overall survival [OS]) • Tumor response evaluation via Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1) • Clinical benefit assessment via quality of life (QoL) scale (EORTC-QLQ-C30 [European Organization for Research and Treatment of Cancer Quality of Life Questionnaire], and PAN-26 module)	Efficacy Objectives • 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) • ~~Clinical benefit assessment via quality of life (QoL) scale (EORTC-QLQ-C30 [European Organization for Research and Treatment of Cancer Quality of Life Questionnaire], and PAN-26 module)~~	Remove questionnaire from study objective
18, 47/48	• Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score *EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea,*	• ~~Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score~~ ~~*EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea,*~~	Move EORTC QLQ- C30 and EORTC QLQ- PAN26 to Exploratory Endpoint

	appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score. • Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score *QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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.*	~~*appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score.*~~ ~~• Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score~~ ~~*QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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.*~~	
18, 47/48	The tumor measurement according to RECIST v.1.1 criteria will be reviewed by a qualified independent review board. The review is independent of the on-site tumor evaluation performed during study conduct.	The tumor measurement according to RECIST v.1.1 criteria will be reviewed by a qualified independent review board. The review is independent of the on-site tumor evaluation performed during study conduct.	Move EORTC QLQ- C30 and EORTC QLQ- PAN26 to Exploratory Endpoint

		Exploratory Endpoints: • Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score *EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score.* • Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score *QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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.	
57, 58, 59	Note: Assessments of laboratory performed 1 day prior to treatment is acceptable.	Note: Assessments of laboratory parameters performed 1 day prior to treatment is acceptable.	Addition of "parameters" for clarity.
	7.14.3 Baseline documentation of 'target' and 'non-target' lesions … Target Lesions: • Select largest reproducibly measurable lesions. If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be	7.14.3 Baseline documentation of 'target' and 'non-target' lesions … Target Lesions: • Select largest reproducibly measurable lesions. If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be measured	Addition of "measured" for clarity
22, 51	**Exclusion Criteria** 8. Laboratory tests (hematology, chemistry) outside specified limits: a) WBC ≤ 3 x 10^3/mm^3 b) ANC ≤ 1.5 x 10^3/mm^3 c) Platelets ≤ 100.000/mm^3	**Exclusion Criteria** 8. Laboratory tests (hematology, chemistry) outside specified limits: a) WBC ≤ 3 x 10^3/mm^3 b) ANC ≤ 1.5 x 10^3/mm^3 c) Platelets ≤ 100,000/mm^3	Corrected typo in the number 100,000
Statistical Considerations:			
25	**Sample Size Determination and Rationale:** … The sample size is event-driven to collect a pre-specified number of primary efficacy outcomes. Based on the sample size calculation, the primary endpoint analysis will require 167 events (deaths) for 196 subjects. This sample size is sufficient to detect a 40% reduction 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	**Sample Size Determination and Rationale:** … The sample size is event-driven to collect 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) for 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	Calculate Sample Size for PFS as one of the Primary Endpoints

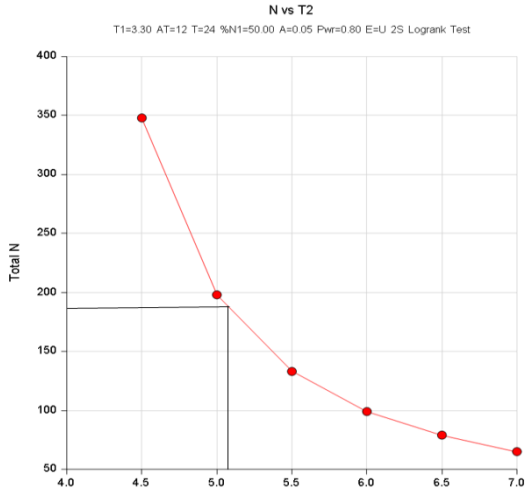
	and an overall significance level of 0.05 two sided test. Sample size estimation is depicted in Figure 9-1, total sample size requirement vs. the median survival time (month) in the treatment arm.	40% reduction in the risk of death in Arm A, as compared with Arm B (hazard ratio, 0.60) using a 2-sided 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 progressive free survival in the risk of disease progression 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 is depicted in Figure 9-1and Figure 9-2, total sample size requirement vs. the median survival time (month) in the treatment arm.	
25/26	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 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.	Calculate Sample Size for PFS as one of the Primary Endpoints
9	Statistical Considerations		

98	**Description of Study Endpoints** **Secondary Efficacy Endpoints** 4. Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score *EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score.* 5. Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score *QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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*	**Description of Study Endpoints** **Secondary Efficacy Endpoints** ~~1. Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score~~ ~~*EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score.*~~ ~~2. Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score~~ ~~*QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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-*~~	Move EORTC QLQ- C30 and EORTC QLQ- PAN26 to Exploratory Endpoint

	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.	~~*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.*~~ **<u>Exploratory</u> Endpoints** • Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score *EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score.* • Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life	

		Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score *QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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.*	
98	**9.3 Sample Size Determination and Rationale** … The sample size is event-driven to collect a pre-specified number of primary efficacy outcomes. Based on the sample size calculation, the primary endpoint analysis will require 167 events (deaths) from the 196 subjects. This sample size is sufficient to detect a 40% reduction 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. Sample size estimation is depicted in Figure 9-1, total sample size requirement vs. the median survival time (month) in the treatment arm. Sample size is estimated using PASS (15) sample size software.	**9.3 Sample Size Determination and Rationale** … The sample size is event-driven to collect a pre-specified number of primary efficacy outcomes. Based on the sample size calculation, the primary endpoint analysis <u>for overall survival</u> will require 167 events (deaths) from the 196 subjects. <u>The primary endpoint analysis for progression-free survival will require 169 events (disease progression) from 182 subjects.</u> This sample size is sufficient to detect a 40% reduction <u>of overall survival</u> 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. <u>This sample size is also sufficient to detect a 35% reduction of progression free survival in the risk of disease</u>	Calculate Sample Size for PFS as one of the Primary Endpoints

		progression 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 9-1, 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 9-2, total sample size requirement vs. the median survival time (month) in the treatment arm. Sample size is estimated using PASS (15) sample size software.	
98	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 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.	Calculate Sample Size for PFS as one of the Primary Endpoints
99	Figure 9-1 Size Plot: Total sample size requirement vs. the median survival time (month) in the treatment arm A.	Figure 9 1: Overall Survival Sample Size Plot: Total sample size requirement vs. the median survival time (month) in the treatment arm A.	Specify the sample size plot for Overall Survival

99	none	Figure 9 2: Progression-Free Survival Sample Size Plot: Total sample size requirement vs. the median survival time (month) in the treatment arm A. 	Create sample size plot for Progression Free Survival
105	**9.8.3 Efficacy Analyses** … **Primary Endpoints:** 1. 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. 2. Overall survival (OS)	**9.8.3 Efficacy Analyses** … **Primary Endpoints:** 1. Overall survival (OS) Overall survival time is defined as time from randomization to death from any cause or last day known to be alive. 2. Progression Free Survival (PFS)	Order Overall Survival to be the first primary endpoint; PFS to be the second primary endpoint in order

	Overall survival time is defined as time from randomization to death from any cause or last day known to be alive.	Progression Free Survival time is defined as the time from randomization to either first observation of progressive disease or occurrence of death.	
106	**Primary Endpoints** … PFS and OS will be compared between the treatment groups using Cox proportional hazards model with the stratification factors included in the model. The hazard ratio for treatment effect and its 95% CI will be estimated. The validity of the proportional hazards assumption will first be checked by defining a time dependent covariate and employing it in the model. If the assumption of proportional hazards holds then the estimate for the time-dependent covariate will not differ significantly from zero. If the proportional hazards assumption is violated, then the adjusted hazard ratio arising from inclusion of the time-dependent covariate will be reported. The Score likelihood test (i.e., which is equivalent to log-rank test) from the Cox proportional hazards model will be used to assess the difference between treatment arms. In addition, the Kaplan-Meier method will also be used to depict the median time to death from any cause for the treatment groups.	**Primary Endpoints** … OS and PFS will be compared between the treatment groups using stratified log-rank test with the stratification factors included in the model. The differences for treatment effect and its 95% CI will be estimated. ~~The validity of the proportional hazards assumption will first be checked by defining a time dependent covariate and employing it in the model. If the assumption of proportional hazards holds then the estimate for the time-dependent covariate will not differ significantly from zero.~~ ~~If the proportional hazards assumption is violated, then the adjusted hazard ratio arising from inclusion of the time-dependent covariate will be reported.~~ ~~The Score likelihood test (i.e., which is equivalent to log-rank test) from the Cox proportional hazards model will be used to assess the difference between treatment arms.~~ In addition, the Kaplan-Meier method will also be used to depict the median time to death from any cause for the treatment groups.	Proportional hazards model removed – replaced with stratified log-rank test.

106	**Secondary Endpoints:** … 4. Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score 5. Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score …	**Secondary Endpoints:** … ~~4. Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) Score~~ ~~5. Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ-PAN26) Score~~ … **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 Similar analysis methods used for secondary endpoints will be applied to the analysis of the exploratory endpoints. Detailed analysis methods will be described in the SAP.	Move EORTC QLQ- C30 and EORTC QLQ- PAN26 to Exploratory Endpoint
12	Data and Safety Monitoring Board (DSMB)		
112	…	…	Futility is not planned for DSMB.

	The DSMB will monitor the safety of the trial from the beginning and at approximately six month intervals based on enrolment thereafter; the DSMB will also assess the study for futility once approximately 60% (~167 events) have been randomized on the trial and followed up for at least 48 weeks or have deaths, whichever comes first.	The DSMB will monitor the safety of the trial from the beginning and at approximately six month intervals based on enrolment thereafter~~; the DSMB will also assess the study for futility once approximately 60% (~167 events) have been randomized on the trial and followed up for at least 48 weeks or have deaths, whichever comes first~~.	
	Other editorial changes to be in line with the order of primary endpoints: 1. OS, 2. PFS.		

Protocol Synopsis

Name of Sponsor/Company: SynCore Biotechnology Co., Ltd.	
Name of Study Product: EndoTAG-1 (paclitaxel in cationic liposomes)	
Protocol Number: CT 4006	**Indication:** Unresectable Locally Advanced/ Metastatic Adenocarcinoma of the Pancreas
Title of Study: 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	
Study Center(s): Up to 100 multinational centers	
Planned Number of Subjects: A total of 218 (109 per arm) subjects will be randomized.	**Study Development Phase:** Phase 3
Indication for Use: Lipid Complexed Paclitaxel (EndoTAG-1), in combination with gemcitabine, is indicated for the combination regimen in patients with locally advanced and/or metastatic adenocarcinoma of the pancreas who are eligible for second-line therapy after failing first-line therapy with FOLFIRINOX.	
Study Rationale: 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;	

Name of Sponsor/Company: SynCore Biotechnology Co., Ltd.	
Name of Study Product: EndoTAG-1 (paclitaxel in cationic liposomes)	
Protocol Number: CT 4006	**Indication:** Unresectable Locally Advanced/ Metastatic Adenocarcinoma of the Pancreas

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.

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.

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)

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

Endpoints:

Primary Efficacy Endpoints:

- 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.

Secondary Efficacy Endpoints:

Name of Sponsor/Company: SynCore Biotechnology Co., Ltd.	
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- Percentage of subjects with Objective Response (OR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1)*
  Percentage of subjects with objective response is based on assessment of complete response (CR) or partial response (PR) according to RECIST v.1.1.

- Duration of Response (DR)*
  Duration of Response is defined as the time from the first documentation of objective tumor response (date of the first CR or PR) to objective tumor progression or death due to any cause.

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

- Serum Carcinoma Antigen 19-9 (CA 19-9) response rate
  Responders are defined as subjects with a reduction in CA 19-9 levels by least 50% from baseline to the end of cycle 1 (or end of full treatment course).

*The tumor measurement according to RECIST v.1.1 criteria will be reviewed by a qualified independent review board. The review is independent of the on-site tumor evaluation performed during study conduct.

Exploratory Endpoints:

- Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score
  EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score.

- Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score
  QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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.

Safety Assessments:

Name of Sponsor/Company: SynCore Biotechnology Co., Ltd.	
Name of Study Product: EndoTAG-1 (paclitaxel in cationic liposomes)	
Protocol Number: CT 4006	**Indication:** Unresectable Locally Advanced/ Metastatic Adenocarcinoma of the Pancreas

Safety will be assessed based on the following assessments:

- 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

Trial 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/m2 twice weekly plus gemcitabine 1000mg/m² once weekly, for 1 cycle (8 weeks) consisting of 3 weeks of treatment 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 in absence of disease progression or unacceptable toxicity. Subsequent Treatment Cycles (8 weeks/ cycle) will be administered as 3 weeks of treatment and 1 week rest followed by 3 weeks of treatment and 1 week rest.
- **Arm B**: Treatment with gemcitabine 1000mg/m² once weekly, for 1 cycle (8 weeks) consisting of 3 weeks of treatment 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 in absence of disease progression or unacceptable toxicity. Subsequent Treatment Cycles (8 weeks/ cycle) will be administered as 3 weeks of treatment and 1 week rest followed by 3 weeks of treatment and 1 week rest.

Name of Sponsor/Company: SynCore Biotechnology Co., Ltd.	
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The randomization will be stratified by

- Subjects with locally advanced vs metastatic pancreatic cancer
- Subjects with 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.

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

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 for the study is provided in Table 0-1 and Table 0-2.

Duration of Treatment:

- **Screening Phase (Screening to Baseline):** Up to 14 days
- **Treatment Phase:**
  - First Treatment Cycle:

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- Treatment Group A: 8 weeks or potentially longer in the event of postponements (a total of 6 weekly infusions of gemcitabine and 12 twice weekly infusions of EndoTAG-1).
- Treatment Group B: 8 weeks or potentially longer in the event of postponements (a total of 6 weekly infusions of gemcitabine).

  - Subsequent Treatment Cycles: Subjects will be eligible for continuing treatment with 3 weeks of treatment 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.

- **Follow-Up Phase:** Follow-up visits will be performed every 8 weeks until death or end of the study, whichever comes first.

Inclusion Criteria: Potential subjects are required to meet all of the following criteria for enrollment into the study and subsequent randomization:

1. Age ≥ 18 years
2. Written informed consent
3. Histologically or cytologically confirmed adenocarcinoma of the pancreas
4. Metastatic or locally advanced disease that is considered unresectable
5. Measurable / assessable disease according to RECIST v.1.1
6. Documented disease progression on first line FOLFIRINOX
7. Negative pregnancy test
8. Both male and female patients and their partners of childbearing potential must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, tubal sterilization or vasectomy) or must practice complete abstinence from intercourse of reproductive potential during the whole treatment duration and for at least 6 months after last treatment for arm A and arm B (excluding women who are not of childbearing potential and men who have been sterilized).
9. ECOG performance status 0 or 1

Exclusion Criteria: Potential subjects meeting any of the following criteria will be excluded from enrollment and subsequent randomization:

1. Cardiovascular disease, New York Heart Association (NYHA) III or IV
2. History of severe supraventricular or ventricular arrhythmia

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3. History of coagulation or bleeding disorder
4. History of acute myocardial infarction within 6 months before randomization
5. History of congestive heart failure
6. Acute or chronic inflammation (autoimmune or infectious)
7. Significant active/unstable non-malignant disease likely to interfere with study assessments
8. Laboratory tests (hematology, chemistry) outside specified limits:
   d) WBC $\leq 3 \times 10^3/mm^3$
   e) ANC $\leq 1.5 \times 10^3/mm^3$
   f) Platelets $\leq 100{,}000/mm^3$
   g) Hb ≤ 9.0 g/dl (≤ 5.6 mmol/l)
   h) aPTT > 1.5 x ULN
   i) Serum creatinine > 2.0 mg/dl (> 176.8 µmol/l)
   j) AST and/or ALT > 2.5 x ULN; for patients with significant liver metastasis AST and/or ALT > 5 x ULN
   k) Alkaline phosphatase > 2.5 x ULN
   l) Total bilirubin > 2 x ULN
   m) Albumin < 2.5 g/dL
9. Clinically significant ascites
10. Any anti-tumor treatment (except FOLFIRINOX as the first-line therapy) for pancreatic adenocarcinoma before enrollment.

    Note: Patients who have undergone surgical interventions for pancreatic adenocarcinoma will be eligible.
11. Any radiotherapy for pancreatic adenocarcinoma before enrollment except for treatment of bone metastases if target lesions are not included in the irradiated field
12. Major surgery < 4 weeks prior to enrollment
13. Pregnant or nursing
14. Investigational medicinal product < 4 weeks of enrollment
15. Documented HIV history
16. Active hepatitis B infection requiring acute therapy

    Note: Subjects infected by the hepatitis B virus will be eligible for the study if they have no signs of hepatic decompensation and meet the liver function tests eligibility criteria.

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17. Known hypersensitivity to any component of the EndoTAG-1 and/or gemcitabine formulations
18. History of malignancy other than pancreatic cancer < 3 years prior to enrollment, except non-melanoma skin cancer or carcinoma in situ of the cervix treated locally
19. Vulnerable populations (e.g. subjects unable to understand and give voluntary informed consent)

Test Product, Dose and Mode of Administration:

Test product: EndoTAG-1

Mode of administration: Intravenous infusion

Dose: 22 mg/m² twice weekly

Study Treatment

Arm A:

- Treatment cycle 1: EndoTAG-1 will be given at a dose of 22 mg/m² as an intravenous infusion which should be started slowly and increased to a maximum of 1.5 ml/min (15 min at 0.5 ml/min, 15 min at 1.0 ml/min. and thereafter 1.5 ml/min.) on days 1, 4, 8, 11, 15, 18, 29, 32, 36, 39, 43 and 46 plus gemcitabine 1000 mg/m², 30 min. i.v. infusion on days 4, 11, 18, 32, 39, and 46 of cycle 1 until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent
- Subsequent treatment cycles: EndoTAG-1 on days 1, 4, 8, 11, 15, 18, 29, 32, 36, 39, 43 and 46 plus gemcitabine on days 4, 11, 18, 32, 39, and 46 of all subsequent cycles, until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent

Arm B:

- Treatment cycle 1: gemcitabine 1000 mg/m², 30 min. i.v. infusion on days 4, 11, 18, 32, 39, and 46 of cycle 1 until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent
- Subsequent treatment cycles: gemcitabine on days 4, 11, 18, 32, 39, and 46 of all subsequent cycles, until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent

Dose adjustment in the event of toxicities:

The doses and timing of treatment will be modified based on toxicities experienced by the subject. Dose modification and retreatment are outlined below:

Dose Modifications for EndoTAG-1:

Criteria for Dose Modifications

- Grade 4 neutropenia lasting 7 or more days

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- Febrile neutropenia
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with significant bleeding or requiring transfusion
- Grade ≥ 3 stomatitis/vomiting/diarrhea
- Other ≥ Grade 3 and 4 toxicities [a, b]

[a] *Except Grade 3 fatigue/asthenia or transient arthralgia/myalgia for which no dose modification is required.*

[b] *To be adjusted as medically indicated after discussion between Investigator and Sponsor*

If any of the above mentioned toxicity criteria are present, no study medication is to be administered at this visit. If the toxicity criteria are no longer fulfilled at the next scheduled visit, EndoTAG-1 is to be administered at a reduced dose of 11 mg/m². If the subject tolerates treatment at the reduced dose (i.e. does not develop any of the above mentioned toxicities), the EndoTAG-1 dose should be re-escalated to 22 mg/m². If re-escalation is not tolerated by the subject, the dose is to be permanently reduced to 11 mg/m². The attempt for re-escalation of the EndoTAG-1 dose is to be made only once throughout the study. Subjects not tolerating treatment even after dose reduction will be taken off study.

Dose Modifications for Gemcitabine:

Dose Modifications for Hematologic Adverse Reactions

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥ 1000	And	≥100,000	100%
500-999	Or	50,000 – 99,999	75%
<500	Or	<50,000	Hold

Dose Modifications for Non-Hematologic Adverse Reactions

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Note: Withhold gemcitabine or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

If a subject fails to meet criteria for retreatment on the day the next treatment is scheduled, treatment should be omitted and the subject will be re-evaluated at least weekly. Treatment may

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be omitted for a maximum of 2 weeks. If treatment is omitted for >1 week, a new cycle should be started upon continuation of treatment. Any subject who fails to recover from a treatment related adverse event to baseline or Grade 2 within 2 weeks of scheduled retreatment will be withdrawn from the study with the exception of subjects who benefit from study treatment (non-progressive disease according to RECIST v.1.1), who may continue treatment on study after consultation and approval of the Sponsor.

Subjects assigned to Arm A (EndoTAG-1 plus Gemcitabine)

Subjects may start a new cycle of combination therapy if ANC is > 1,500/mm^3, platelets are > 100,000/mm^3 and treatment-related non-hematologic adverse event including neuropathy has resolved to baseline or Grade 2. Subjects with Grade 2 neuropathy will not be retreated until resolved to Grade 1.

Note: Subjects on treatment arm A who require discontinuation of gemcitabine will not continue on single-agent EndoTAG-1 alone. However, subjects in Treatment Arm A who require discontinuation of EndoTAG-1 due to toxicity may continue on gemcitabine monotherapy. Subjects on Arm B (gemcitabine alone) will not be offered treatment with EndoTAG-1 at the time of discontinuation (no cross-over allowed).

Statistical Considerations:

Sample Size Determination and Rationale:

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 collect 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) for 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 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 progressive free survival in the risk of disease progression 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 is depicted in Figure 9-1 and Figure 9-2, total sample size requirement vs. the median survival time (month) in the treatment arm.

A dropout rate of 10% is factored in the sample size calculations for a total sample size of 218 subjects. Sample size is estimated using PASS (15) sample size software.

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

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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.

Randomization and Stratification:

Prior to randomization, subjects will be stratified by extent of disease (subjects with locally advanced and metastatic pancreatic cancer) and the performance status (ECOG performance status 0 and 1). Then they will be randomized with a 1:1 ratio.

Analysis Populations:

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 and secondary endpoints.

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 **Safety population** is defined as any subject receiving the treatment after randomization. This population will be used for the analysis of safety parameters.

Analysis Considerations:

A detailed Statistical Analysis Plan (SAP) accompanies the protocol and any amendments to the SAP will be finalized prior to final database lock. Any significant changes to the analyses described in this protocol will be highlighted in the SAP and the Clinical Study Report.

Analysis of time-to-event parameters (OS, PFS): times to event will be estimated together with the respective 95% CIs for each treatment group using the Kaplan-Meier method. The log-rank test (stratification factors ECOG and TNM) will be calculated for comparison of OS and PFS for the combination therapy treatment versus the gemcitabine monotherapy group.

Tumor response: For each subject, the overall response to treatment after the initial 7-week treatment cycle will be assessed according to RECIST v.1.1 criteria. The proportions of subjects with CR, PR, OR, SD, PD, disease control (CR, PR or SD), at the end of cycle 1, as well as the overall response to treatment, will be calculated for each treatment group and presented with exact 95% confidence intervals (CIs).

Change from baseline in CA 19-9: The proportion of subjects with a change from normal to abnormal, no change, or a change from abnormal to normal, and the proportion of subjects with a response will be calculated. Exact 95% CIs will be calculated for the proportion of subjects with a change from abnormal to normal and for the proportion of subjects with a response.

Change from baseline in QLQ-C30 and PAN-26: Differences in proportions between treatment groups will be estimated and exact 95% CIs will be calculated for these estimates. These analyses will be performed for all individual QoL scores, QLQ-C30 Global Health score and for the PAN-26 score at the end of treatment cycle 1 and also for the full treatment course.

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List of Abbreviations

Abbreviation	Definition
AE(s)	Adverse Event(s)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
API	Active Pharmaceutical Ingredient
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BSA	Body Surface Area
BW	Body Weight
CL	Clearance
C_{max}	Maximum Plasma Concentration
CR	Complete Response
eCRF	Electronic Case Report Form
CRO	Clinical Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
DOPC	dioleoyl-phosphatidylcholine
DOTAP	dioleoyl-trimethylammonium-propane
DOTAP-Cl	dioleoyl-trimethylammonium-propane chloride
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
GCP	Good Clinical Practice
GEM	gemcitabine
GGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
HDL	High-density Lipoprotein
Hct	Hematocrit
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug

Abbreviation	Definition
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
LAR	Legally Acceptable Representative
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MRI	Magnetic Resonance Imaging
NCI-CTC	National Cancer Institute - Common Terminology Criteria
NOAEL	no observed adverse effect level
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PP	Per-Protocol
PR	Partial Response
PT	Prothrombin
QoL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	Stable Disease
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TNBC	Triple-Negative Breast Cancer
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell
WOCBP	Women Of Child Bearing Potential

Table 0-1: 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 0-2: 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]/EO	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

1 Introduction

1.1 Background Information

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.

1.2 EndoTAG-1

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.

EndoTAG-1 was first developed by Munich Biotech AG (Germany) under the names LipoPac and MBT-0206 and by Medigene AG under the name of EndoTAG-1. Since 2013, development and global commercialization of EndoTAG-1 is executed by SynCore Biotechnology Co., Ltd.

EndoTAG-1 is formed by the synthetic cationic lipid dioleoyl-trimethylammonium-propane chloride (DOTAP-Cl) and the natural neutral phospholipid dioleoyl-phosphatidylcholine (DOPC). In an aqueous solution of trehalose, liposomal membranes embedded with paclitaxel are assembled.

1.2.1 Non-clinical studies using EndoTAG-1

EndoTAG-1, when given intravenously in a variety of syngeneic and xenograft tumor models in mice and hamster, showed a pronounced higher uptake into tumor tissue compared to normal tissue. In all models tested, EndoTAG-1 led to a significantly reduced tumor growth activity compared to treatment with standard paclitaxel, independent of tumor type, animal species and immune status. In addition, the rate of metastasis was significantly decreased by EndoTAG-1 compared to standard paclitaxel. Furthermore, EndoTAG-1 was shown to be effective in paclitaxel-resistant tumors in animals.

An increased anti-tumor activity in animals was observed when EndoTAG-1 was combined with other cytostatic or cytotoxic agents. Combination therapy (e.g. EndoTAG-1 + gemcitabine) showed enhanced tumor regression, reduction of lymph node metastases and absence of liver metastases compared to either monotherapy. In vitro, combination therapies of Endo TAG-1 with chemotherapeutics showed complete or concentration-dependent additivity, thus supporting the in vivo data.

Mode-of-action studies in rodents demonstrated the neovascular targeting properties of EndoTAG-1. A strong decrease of the endothelial proliferation index in the tumor periphery as well as a reduction of the tumor perfusion index and an increase of endothelial cell apoptosis was observed. These results indicate a potential dual mode-of-action of EndoTAG-1 by combining anti-neovascular and anti-tumor effects (Eichhorn et al 2010, Strieth et al 2008, Strieth et al 2004, Schmitt-Sody et al 2003).

Toxicology

The toxicological profile of EndoTAG-1 has been evaluated in single- and repeated-dose toxicity studies in mice, rats and dogs covering treatment periods of up to 26 weeks.

In an acute toxicity study in mice mortality was observed at 5.4 mg/kg BW liposomal paclitaxel. The same mortality was reported in the control group using empty liposomes and was most likely due to the large volumes of injected suspended lipid complexes. No other findings were reported in the acute toxicity studies.

In subchronic toxicity studies in rats the high dose EndoTAG-1 group (1.5 mg/kg BW liposomal paclitaxel) showed slight weight loss and reduction of white blood cells. The main histopathological finding was hypocellularity of the hematopoetic bone marrow in about one third of the rats in this dose group. The effects were reversible and resolved during recovery.

Acute, subchronic and chronic repeated dose toxicity studies have been performed in dogs. In the 14-day and 28-day studies liposomal paclitaxel doses up to 1.7 mg/kg BW

and 1.5 mg/kg BW, respectively, per application were given daily or every other day. At higher doses reduced food uptake accompanied by a moderate but continuous reduction in body weight was observed and lesions were found in the gastrointestinal tract - findings which are attributed to the action of paclitaxel. With daily treatment, lethal toxicity was observed in all dose groups. When dosed at 2-day intervals, treatment was tolerated better and only some animals of the higher dose groups died. In the 90-day and 180-day studies, doses up to 1.2 mg/kg BW were applied twice a week, resulting in a total of 22 to 27 and 46 applications, respectively. Due to severe toxicities including mortality observed in the high dose group, treatment was interrupted and, in part, reduced to one application per week.

A "no observed adverse effect level" (NOAEL) could not be established in studies covering a treatment period of 3 or 6 months, which is common for cytostatic and cytotoxic drugs with low therapeutic index. The non-clinical toxicity studies indicate that the haematopoietic system, the gastrointestinal tract including the liver and the gall bladder and the male gonads are the potential target organs in humans. Microscopic lesions were seen mainly in areas of high tissue turn-over such as the gastrointestinal tract and the testes. Based on acute findings (hemorrhagic pulmonary edema) observed in a number of animals that died prematurely in the subchronic and chronic toxicity studies in dogs, the lung represents an additional target organ. During clinical application of EndoTAG-1 the function of these organ systems should be closely monitored. Other known side effects of standard paclitaxel were not observed during administration of EndoTAG-l.

Pharmacokinetics

The pharmacokinetic profile of EndoTAG-1 has been established in single dose studies in mice and rats and in repeated dose toxicokinetic studies in rats and dogs. The highest systemic exposure of paclitaxel from EndoTAG-1 was observed in humans and dogs, and the lowest in rats and mice. These findings were in line with the clearance rates observed, which were low for non-rodents (humans/ dogs) and high for rodents (rats/ mice).

A linear pharmacokinetic relationship was determined for the administered EndoTAG-1 dose and the C_{max} and AUC of paclitaxel in rats and dogs. The pharmacokinetic profiles of paclitaxel from EndoTAG-1 compared to standard paclitaxel in rodents seemed to be almost identical at lower doses (1.1 mg/ kg BW liposomal paclitaxel), whereas at higher doses (5 mg/ kg BW liposomal paclitaxel) Cmax and AUC values of paclitaxel from EndoTAG-1 were markedly lower. No comparative studies have been performed in non-rodents.

In vitro and in vivo studies demonstrated comparable metabolism of paclitaxel for EndoTAG-1 and standard paclitaxel. Both agents resulted in similar biodistribution patterns and kinetics in female rats. The highest concentration of paclitaxel was found in the liver, but marked concentrations were also observed in kidney, lung, heart, spleen

and adrenal gland. Paclitaxel was mainly excreted in bile (-88% of dose) and excretion was almost completed after 72 hours for both EndoTAG-1 and standard paclitaxel.

The pharmacokinetic profile of the cationic liposomal constituent DOTAP is characterized by a linear relationship between the administered EndoTAG-1 dose and C_{max} and AUC. In contrast to paclitaxel a later C_{max} was observed for DOTAP. It appears to be slowly distributed and is incompletely cleared from systemic blood circulation. The results of the biodistribution study in female rats showed that a large amount of DOTAP is transiently distributed to the lungs and relatively high levels are maintained until a marked decrease of DOTAP occurred between 6-24 hours. In contrast, liver, kidneys and spleen showed a gradual increase of DOTAP levels up to 6-24 hours. DOTAP was mainly excreted in the urine (78% of dose) and excretion occurred rather slowly. After 5 days, 9.2% of the dose was still present in the body. Consequently, accumulation of DOTAP was observed in the plasma of rats and dogs when EndoTAG-1 was administered twice per week for 26 weeks, but was not associated with a notable increase in toxicities.

In vitro studies with human liver microsomes suggested either the absence of or only a weak Cytochrome P450 inhibition potential for DOTAP, whereas Cremophor EL, the excipient of standard paclitaxel, turned out to be a very potent Cytochrome P450 inhibitor.

1.2.2 Clinical studies using EndoTAG-1

A total of 460 subjects with a variety of solid tumors have been treated with EndoTAG-1 during participation in clinical studies.

Nine clinical studies (phase 1/2) were initiated by the company Munich Biotech AG (MBT), which originally started the development of EndoTAG-1. Various doses (2.63 - 66 mg/m^2 liposomal paclitaxel), infusion speeds (up to 2.5 mL/min) and schedules (daily to weekly, for up to nine weeks) were examined in these studies. In these studies, a total of 163 subjects were treated with EndoTAG-1. EndoTAG-1 was usually given as a monotherapy except for one study in NSCLC (combination with carboplatin) and one study in gastrointestinal cancer (combination with 5-FU).

At MediGene AG, three phase 2 trials have been conducted:

- CT4001, an open-label, randomized, controlled Phase 2 study in 200 subjects with locally advanced or metastatic pancreatic cancer, was conducted to assess the safety and efficacy of a combination therapy of gemcitabine (Gemzar®) and EndoTAG-1 at three different dose levels (corresponding to 11, 22 and 44 mg/m^2 paclitaxel) versus gemcitabine monotherapy. EndoTAG-1 in combination with gemcitabine was generally well tolerated, corroborating the favorable safety profile observed in the Phase 1/2 studies. In terms of efficacy, the results indicate a survival benefit in subjects receiving EndoTAG-1 in combination with gemcitabine compared to gemcitabine alone, both for progression-free and overall survival.

- CT4002 was an open-label, randomized, controlled Phase 2 study to assess the efficacy and safety of treatment with infusions of EndoTAG-1 monotherapy (44mg/m² paclitaxel) twice per week or weekly infusions of EndoTAG-1 (22 mg/m² paclitaxel) in combination with standard paclitaxel (70 mg/m²) compared with paclitaxel monotherapy (90 mg/m² weekly) in 140 subjects with locally relapsed and/or metastatic triple receptor-negative breast cancer (TNBC). Treatment with EndoTAG-1 alone or in combination was well tolerated with manageable adverse events. The PFS rate at week 16, the primary efficacy endpoint, was 59.1% on combination therapy, 34.2% on EndoTAG-1 and 48.0% on paclitaxel. Exact one-sided 95% CIs revealed that the hypothesis H0 (PFS rate ≤ 30%) could be rejected for the EndoTAG-1/paclitaxel combination group only. For a subgroup of subjects with confirmed TNBC, ECOG 0/1 at baseline and receiving first-line therapy for advanced disease, a median OS of 17.8, 11.9, and 10.1 months was achieved by the three treatment groups, respectively. These results indicate that EndoTAG-1 in combination with standard paclitaxel could be an efficacious and safe first-line therapy for patients with advanced TNBC.
- CT4003 was an open-label, uncontrolled Phase 2 study evaluating the single-dose and steady-state pharmacokinetics of EndoTAG-1 and its effect on the blood supply and the angiogenesis of hepatic metastases in 20 subjects with a carcinomatous primary tumor other than hepatocellular (HCC), biliary or bile duct carcinoma.

An investigator initiated trial (IJBNeoEndoTAG-1) was conducted at the Institute Jules Bordet in Brussels, Belgium. This study was an open-label, uncontrolled, single- center trial in 15 subjects with HER2-negative breast cancer who were candidates for surgery, including 6 subjects with TNBC. The objective of this study was to evaluate efficacy and safety of neoadjuvant EndoTAG-1 (22 mg/m² paclitaxel) in combination with standard paclitaxel (70 mg/m²) administered as 12 weekly infusions, followed by fluorouracil (500mg/m^2), epirubicin (100mg/m^2) and cyclophosphamide (500mg/m^2) (FEC) administered every 3 weeks for a total of 9 weeks. The safety results were as expected from previous trials. Treatment with EndoTAG-1 plus paclitaxel resulted in significant reduction of MRI-estimated tumor volume and linear tumor size compared with baseline. Overall, a pathologic complete response (pCR) was achieved in 33% of the subjects. Of the 6 subjects with TNBC, 5 subjects achieved pCR.

Safety

Safety data of 163 subjects suffering from various solid tumors are available from phase 1/2 studies. 138 (84.6%) subjects experienced one or more adverse events (AEs), 902 AEs were reported in total. Most of these events were assessed as being causally related to study medication by the investigator (668 of 902, or 74%) and were classified as non-serious (830 of 902, or 92%). The majority of these non-serious adverse drug reactions (ADR's) were of transient nature. Only 20 (2.2 %) AEs were assessed as serious and drug-related by the investigator.

In study CT 4001, AEs were reported in 92% to 100% of subjects in each treatment arm. No unexpected toxicities have been observed. During the first treatment cycle, severe hematological toxicities (grade 3/4 NCI-CTC) related to any study medication occurred in 22, 32 and 40% of subjects in the different GEM+Endo groups (11, 22 and 44 mg/m^2, respectively) compared to 24% on Gem monotherapy. Combination of EndoTAG-1 and Gem resulted in a dose dependent increase of grade 3/4 thrombocytopenia reaching up to 16% and 14% in the two higher dose levels, albeit without clinical symptoms or bleeding complications. At the highest EndoTAG-1 dose level (44mg/m^2 twice weekly), increased rates of grade 3/4 neutropenia (22%) and anemia (12%) were observed. During the first cycle, a total of 7 cases of febrile neutropenia were reported in the two higher GEM+Endo dose levels, including 4 cases of grade 3/4. During additional cycles with GEM+Endo therapy, none was observed. Infusion-related reactions, predominantly pyrexia and chills, were found to a higher extent in GEM+Endo groups, whereas the addition of EndoTAG-1 to Gem did not increase the known liver toxicity of Gem. In the GEM+Endo44 arm, one case of neuropathy was reported in a subject with diabetes, but was considered unrelated to study medication.

AEs resulting in discontinuation of study medication were reported in 4 subjects (8%) in the GEM+Endo11 and 7 subjects (14%) in each of the GEM+Endo22 and GEM+Endo44 group. During the first cycle, 2 subjects (4%) in each of the GEM+Endo11 and GEM+Endo22 group, and 1 subject (2%) in the GEM+Endo44 group died, but deaths were considered not related to study medication. During additional cycles, another 2 subjects of the GEM+Endo11 group had SAEs with fatal outcome. Both events, Staphylococcal sepsis and death from unknown cause, were considered unlikely to be related to study medication.

In study CT4002 safety analysis revealed qualitatively and quantitatively the known toxicities of EndoTAG-1 and standard paclitaxel. AEs were reported in 91% to 100% of subjects in each treatment arm. No unexpected toxicities have been observed. EndoTAG-1 showed a similar safety profile to paclitaxel. On combination treatment, a slight increase in grade 3/4 adverse events was observed compared to either monotherapy, with uncomplicated neutropenia being the most predominant adverse event. Neutropenia was highest among subjects on combination therapy (40%), whereas anemia was predominantly observed in the standard paclitaxel study arm (36%). Grade 3/4 hematological toxicities, especially neutropenia and leucopenia, occurred more often in the combination arm (20% and 7%) compared to either agent alone (4% and 2% for EndoTAG-1 monotherapy, 7% and 0% for standard paclitaxel, respectively) (Awada et al, 2010).

As was observed in CT4001, infusion-related reactions, predominantly pyrexia and chills were found to a higher extent in EndoTAG-1 treatment arms and increased at higher doses. Peripheral sensory neuropathy was observed in 13% of the combination treatment arm compared to 9% and 14% of subjects on EndoTAG-1 monotherapy and

standard paclitaxel, respectively. Severe neurotoxicity was reported for 1 subject (4%) of the standard paclitaxel treatment arm.

In study CT4003 all 20 subjects experienced at least one AE, with a total of 330 AEs reported. 33 AEs of grade 3/4 and 21 SAEs were observed and reported from 11 (55%) subjects. The most frequent AEs were abdominal pain, nausea, vomiting and fatigue in 10 to 14 subjects (50-70%). Hypersensitivity and hyperhidrosis occurred in 8 subjects each (40%) and were mostly of mild to moderate severity. Hematological toxicities were observed in 4 subjects (20%), including 3 events of anemia and 1 event each of neutropenia and leucopenia (both of grade 3 severity). Peripheral sensory neuropathy was reported for 3 subjects (15%). No AE with a severity of grade 4 was reported.

Pharmacokinetics

The pharmacokinetic properties of EndoTAG-1 were determined in three phase 1/2 dose escalation studies (CTLP01, CTLP05 and CTLP06) exploring several dose levels (2.63-66 mg/m^2 paclitaxel) and application regimen (2-5 times per week) and in study CT4003.

Results of studies CTLP01, CTLP05 and CTLP06 revealed that the maximum plasma concentrations and extents of exposure of paclitaxel and DOTAP, administered as EndoTAG-1, increased with the dose. Data were too limited to assess whether the increase is proportional. The clearance of paclitaxel and DOTAP remained constant with increasing doses, with higher clearance levels observed for paclitaxel compared to DOTAP. There was no indication for paclitaxel accumulation in plasma at any dose level or application regimen studied. Although DOTAP is cleared from the plasma slowly, there was also no evidence for accumulation of DOTAP.

In study CT4003 reliable PK-profiles were obtained for paclitaxel and DOTAP after single dose and in steady state following intravenous infusion of EndoTAG-1 (22 mg/m^2 twice weekly for 25 days). The pharmacokinetic parameters observed for paclitaxel and DOTAP confirmed previous results with 22 mg/m^2 EndoTAG-1 from early clinical trials (CTLP05, CTLP06). The mean maximum plasma concentration of paclitaxel was comparable after single dose and in steady state. The extent of exposure showed a small increase from the first to the last dose. The mean maximum plasma concentration of DOTAP increased from the first to the last dose and the extent of exposure increased more pronounced compared to paclitaxel. Distribution and elimination kinetics of EndoTAG-1 appear to be largely comparably to standard paclitaxel at lower dose levels. Only minor accumulation has been observed for paclitaxel and DOTAP, suggesting that no considerable saturation of distribution or elimination systems occurred. Finally, consistent gender-specific differences have not been observed with respect to the pharmacokinetics of paclitaxel and DOTAP (Fasol et al, 2011).

The pharmacokinetic parameters of EndoTAG-1, paclitaxel and DOTAP were evaluated using the pooled data collected from three phase 1/2 dose-escalation studies

(CTLP01, CTLP05 and CTLP06) and one phase 2 study (CT4003). The results are presented in report titled, Pooled Analyses of Human Pharmacokinetic data of EndoTAG-1 dated 28-Feb-2017.

Efficacy

In their phase 1/2 studies, Munich Biotech AG included patients with hormone-refractory prostate cancer (CTLP01), unresectable locally advanced or metastatic gastrointestinal (CTLP05) or colorectal cancer (CTLP10) and metastatic breast cancer (CTLP09) applying doses between 2.63 and 66 mg/m^2 liposomal paclitaxel in various regimen of up to 9 weeks treatment. Subjects were evaluated for overall tumor response only, survival data were not collected. Complete responses were not reported. Partial responses were observed in 3 (8%, CTLP09) and 1 (3%, CTLP010) subjects, stable disease was seen in 13 (36%, CTLP09), 3 (8%, CTLP010) and 4 (14%, CTLP05) of the subjects. Accordingly the clinical benefit rate was 44% and 11% in CTLP09 and CTLP10, respectively. The effect on tumor stabilization was most distinct in subjects with metastatic breast cancer (CTLP09) with a dose-dependent effect on the rate of subjects with non-progressive disease (33% at 22 mg/m^2, 56% at 44 mg/m^2). In study CTLP01, PSA levels remained stable in the majority of subjects during treatment, but increased during the follow-up period. 1/12 (8.33%) of subjects showed stable disease (reduction of PSA levels > 50%) after 43 days.

In summary, disease stabilization and partial response has been observed in some of the subjects. However, subject numbers were small and studies were conducted without comparator(s). Phase II studies of MediGene AG were conducted in patients with advanced pancreatic cancer (CT4001), triple receptor-negative breast cancer (CT4002) and hepatic metastases from a carcinomatous primary tumor (CT4003).

In study CT4001, 3 different dose levels of EndoTAG-1 (11, 22 and 44 mg/m^2 liposomal paclitaxel) in combination with gemcitabine (GEM+Endo) were compared to gemcitabine monotherapy (GEM) in 200 subjects (50 subjects in each study arm) with unresectable locally advanced or metastatic pancreatic adenocarcinoma. At the time of analysis 161 subjects have died. Median overall survival was 7.2 months on GEM monotherapy compared to 8.4, 8.7 and 9.4 months in the GEM+Endo cohorts (11, 22 and 44 mg/m^2, respectively). Median PFS reached 2.7 months compared to 4.1, 4.6 and 4.4 months and the disease control rate after the first treatment cycle was 43% compared to 60, 65 and 52%, respectively. Accordingly, both the 6- and 12-month survival rates were higher in all GEM+Endo groups than in the GEM group (Löhr et al, 2012).

In study CT4002, 140 women with triple receptor negative metastatic or relapsed breast cancer have been randomized to 3 different study arms: EndoTAG-1 (22 mg/m^2 liposomal paclitaxel) in combination with standard paclitaxel (70 mg/m^2), EndoTAG-1 monotherapy (44 mg/m^2 liposomal paclitaxel, twice per week), and standard paclitaxel monotherapy (90 mg/m^2). Each treatment was given for 3 weeks, followed by 1 week of rest. The disease control rate at week 16, after 4 cycles of therapy, was

59% on combination therapy compared to 34% in the EndoTAG-1 and 48% in the standard paclitaxel cohort (Awada et al, ESMO 2010). The clinical benefit rate (complete or partial response at any time and stable disease 2:6 months) on combination of EndoTAG-1 and paclitaxel (n=50 subjects) was 53% compared to 31 and 36% on EndoTAG-1 and paclitaxel monotherapies, respectively (Awada et al, SABCS 2011). PFS was 4.2 compared to 3.4 and 3.7 months, respectively. In the target population of the study, i.e. patients with TNBC, the overall survival was 13.0 months on combination of EndoTAG-1 and paclitaxel versus 11.9 and 10.1 months on EndoTAG-1 and paclitaxel monotherapies, respectively. Subgroup analysis in subjects with advanced TNBC, ECOG performance status 0 or 1 and first line therapy revealed an overall survival of 17.8 months on combination of EndoTAG-1 and paclitaxel versus 12.5 and 10.1 months on EndoTAG-1 and paclitaxel monotherapies, respectively. However, the study was not powered for intergroup comparisons.

Study CT4003 was conducted to evaluate pharmacokinetics of EndoTAG-1 (22 mg/m^2 liposomal paclitaxel, twice a week) and its effect on blood supply and angiogenesis of hepatic metastases in 20 subjects with a carcinomatous primary tumor other than hepatocellular, biliary or bile duct carcinoma. At the beginning of therapy all subjects had stable disease according to modified RECIST 1.1 criteria. The median PFS was 29 days. The effect of EndoTAG-1 on target liver metastases perfusion assessed by CEUS was inhomogeneous, inflow coefficients showed a great intra-individual variability and a trend could not be elaborated. However, changes in perfusion parameters assessed by DCE-MRI were observed. By Day 29, 65% of subjects had decreases in k_{trans}, iAUC60, iAUC90 and iAUC120, supporting the hypothesis of a vascular targeting mode of action of EndoTAG-1 (Fasol et al, 2011).

In conclusion, EndoTAG-1 has shown vascular targeting, vascular disrupting and anti-tumor activity in different tumors in several nonclinical and clinical studies. Therapeutic efficacy was highest when EndoTAG-1 was administered in combination with other chemotherapeutics. Notably, both in pancreatic cancer and advanced TNBC, EndoTAG-1 has shown clinical benefit and the EndoTAG-1/paclitaxel and EndoTAG-1/gemcitabine treatment combination was well tolerated.

Based on the safety and efficacy data collected in these clinical trials, a positive benefit-risk-profile was established for clinical use of EndoTAG-1.

2 Study Objectives and Endpoints

2.1 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.

2.1.1 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)

2.1.2 Secondary Objective

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

2.2 Study Endpoints

2.2.1 Primary Efficacy Endpoints

There are two primary efficacy endpoints for this study:

- 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.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Percentage of subjects with Objective Response (OR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1)*

  Percentage of subjects with objective response is based on assessment of complete response (CR) or partial response (PR) according to RECIST v.1.1.

- Duration of Response (DR)*

  Duration of Response is defined as the time from the first documentation of objective tumor response (date of the first CR or PR) to objective tumor progression or death due to any cause.

- Percentage of subjects with disease control according to RECIST v.1.1*

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

- Serum Carcinoma Antigen 19-9 (CA 19-9) response rate

  Responders are defined as subjects with a reduction in CA 19-9 levels by least 50% from baseline to the end of cycle 1 (or end of full treatment course).

*The tumor measurement according to RECIST v.1.1 criteria will be reviewed by a qualified independent review board. The review is independent of the on-site tumor evaluation performed during study conduct.

2.2.3 Safety Assessments:

Safety will be assessed based on the following assessments:

- 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

2.2.4 Exploratory Endpoints

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

  EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score.

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

  QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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.

3 Investigational Plan

3.1 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 in absence of disease progression or unacceptable toxicity. Subsequent Treatment Cycles (8 weeks/cycle) will be administered as 3 weeks of treatment and 1 week of rest followed by 3 weeks of treatment and 1 week rest.
- **Arm B:** Treatment with gemcitabine 1000 mg/m^2 once weekly, for 1 cycle (8 weeks) consisting of 3 weeks of treatment 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 in absence of disease progression of unacceptable toxicity. Subsequent Treatment Cycles (8 weeks/cycle) will be administered as 3 weeks of treatment and 1 week reast followed by 3 weeks of treatment and 1 week rest.

The randomization will be stratified by

- Subjects with locally advanced vs metastatic pancreatic cancer
- Subjects with 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 and quality of life (EORTC QLQ-C30 and EORTC PAN-26).

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.

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

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.

3.2 Study Center(s)

Up to 100 multinational centers

3.3 Study Population

Study population includes patients with locally advanced and/or metastatic adenocarcinoma of the pancreas who are eligible for second-line therapy after failing first-line therapy with FOLFIRINOX.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

Potential subjects are required to meet all of the following criteria for enrollment into the study and subsequent randomization:

1. Age ≥ 18 years
2. Written informed consent
3. Histologically or cytologically confirmed adenocarcinoma of the pancreas
4. Metastatic or locally advanced disease that is considered unresectable

5. Measurable / assessable disease according to RECIST v.1.1
6. Documented disease progression on first line FOLFIRINOX
7. Negative pregnancy test
8. Both male and female patients and their partners of childbearing potential must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, tubal sterilization or vasectomy) or must practice complete abstinence from intercourse of reproductive potential during the whole treatment duration and for at least 6 months after last treatment for arm A and arm B (excluding women who are not of childbearing potential and men who have been sterilized).
9. ECOG performance status 0 or 1

3.4.2 Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded from enrollment and subsequent randomization:

1. Cardiovascular disease, New York Heart Association (NYHA) III or IV
2. History of severe supraventricular or ventricular arrhythmia
3. History of coagulation or bleeding disorder
4. History of acute myocardial infarction within 6 months before randomization
5. History of congestive heart failure
6. Acute or chronic inflammation (autoimmune or infectious)
7. Significant active/unstable non-malignant disease likely to interfere with study assessments
8. Laboratory tests (hematology, chemistry) outside specified limits:
   a) WBC $\leq 3 \times 10^3/mm^3$
   b) ANC $\leq 1.5 \times 10^3/mm^3$
   c) Platelets $\leq 100{,}000/mm^3$
   d) Hb ≤ 9.0 g/dl (≤ 5.6 mmol/l)
   e) aPTT > 1.5 x ULN
   f) Serum creatinine > 2.0 mg/dl (> 176.8 µmol/l)
   g) AST and/or ALT > 2.5 x ULN; for patients with significant liver metastasis AST and/or ALT > 5 x ULN
   h) Alkaline phosphatase > 2.5 x ULN
   i) Total bilirubin > 2 x ULN

j) Albumin < 2.5 g/dL

9. Clinically significant ascites
10. Any anti-tumor treatment (except FOLFIRINOX as the first-line therapy) for pancreatic adenocarcinoma before enrollment.

    Note: Patients who have undergone surgical interventions for pancreatic adenocarcinoma will be eligible.
11. Any radiotherapy for pancreatic adenocarcinoma before enrollment except for treatment of bone metastases if target lesions are not included in the irradiated field
12. Major surgery < 4 weeks prior to enrollment
13. Pregnant or nursing
14. Investigational medicinal product < 4 weeks of enrollment
15. Documented HIV history
16. Active hepatitis B infection requiring acute therapy

    Note: *Subjects infected by the hepatitis B virus will be eligible for the study if they have no signs of hepatic decompensation and meet the liver function tests eligibility criteria.*
17. Known hypersensitivity to any component of the EndoTAG-1 and/or gemcitabine formulations
18. History of malignancy other than pancreatic cancer < 3 years prior to enrollment, except non-melanoma skin cancer or carcinoma in situ of the cervix treated locally
19. Vulnerable populations (e.g. subjects unable to understand and give voluntary informed consent)

4 Study Schedule

The study is divided into three phases: Screening, Treatment and Follow-up.

- **Screening Phase (Screening to Baseline):** Up to 14 days
- **Treatment Phase:**
  - First Treatment Cycle:
    - Treatment Group A: 8 weeks or potentially longer in the event of postponements (a total of 6 weekly infusions of gemcitabine and 12 twice weekly infusions of EndoTAG-1).
    - Treatment Group B: 8 weeks or potentially longer in the event of postponements (a total of 6 weekly infusions of gemcitabine).
  - Subsequent Treatment Cycles: Subjects will be eligible for continuing treatment with 3 weeks of treatment 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.
- **Follow-Up Phase:** Follow-up visits will be performed every 8 weeks until death or end of the study, whichever comes first.

Procedures to be performed during each of these study phases are described below and provided as a Schedule of Assessments in Table 0-1 and Table 0-2.

4.1 Screening Visit

The subject (or Legally Acceptable Representative (LAR)) will sign and date the informed consent form (ICF) and Health Insurance Portability Accountability Act (HIPAA) authorization (according to site policy and practices) prior to any study-related procedures. A unique identification number (screening number) will be assigned to each subject who has provided written informed consent. The subject screening number will incorporate a two-digit region code (01, 02 or 03...), a three-digit Study Center number (001, 002 or 003….) and a three-digit numeric ID assigned in successive order of entering the study after signing the ICF at each center, beginning with 001 at each site (e.g. 01-001-001).

Subject Screening #:	**XX** -	**YYY** -	**ZZZ**
	XX=Region	YYY=Study Center	ZZZ=Subject Numeric ID

All study centers will be instructed to maintain the study-specific pre-screening, screening and enrollment logs at their sites. If a subject initially fails to meet inclusion/exclusion criteria and is later reconsidered for participation, the subject will be re-consented and assigned a new screening number at the time of re-screening. Subjects who fail their first screening attempt may be re-screened a maximum of once

and may be enrolled if they are found to meet all inclusion and no exclusion criteria when re-screened.

Patients with a clinical diagnosis of unresectable pancreatic adenocarcinoma may be screened. Prior to all screening procedures the investigator is responsible for explaining all aspects of this trial to the patient including potential side effects and alternative treatments available. The investigator must answer all questions by the patient according to his/her best knowledge and must give the patient ample time to consider his/her participation. If – after that - the patient wishes to participate in this trial, he/she must first give written informed consent. Only then may the investigator proceed with the screening procedure.

The following evaluations and examinations have to be done within 14 days prior to randomization, if not stated otherwise:

- Signed informed consent
- Eligibility criteria
- Demographic data, including date of birth, sex, and ethnic origin
- Disease history, including date of first diagnosis and the history of the course of the disease
- Medical and surgical history, including past or concurrent clinically significant disease(s)
- Previous and concomitant medication
- Physical examination, including evaluation of all body systems
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal), and weight and height. For measurement of body temperature, the same type of measurement is to be used throughout the study.
- Performance status (ECOG Performance Status)
- Blood samples for laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry
    - Coagulation parameters
    - Tumor marker CA 19-9
    - Urinalysis
    - Pregnancy test, if female of childbearing potential (serum or urine)
- Tumor imaging: Abdominal CT-scan with i.v. and gastrointestinal contrasts (or MRI), and chest X-ray (or CT or MRI). Thoracic CT- or MRI-scans have to be

done additionally, if target lesions detected by chest X-ray are not clearly defined or not surrounded by aerated lung. Further imaging exams to be done if lesions are suspected in other areas.

***Note**: Assessments of tumor imaging performed 4 weeks prior to randomization is acceptable.*

- Evaluation of detected lesions according to RECIST (version 1.1; *Eisenhauer et al*. 2009)
- Electrocardiogram
- Quality of Life Questionnaires

All screening information will be fully documented in the subject's medical records (i.e., source documents). **If the patient fulfils all of the inclusion criteria and none of the exclusion criteria the patient may be randomized.**

- For consented subjects who do not meet eligibility criteria, a Screen Failure electronic Case Report Form (eCRF) will be completed. The Screen Failure eCRF will contain the following details: the subject identification number, the date of ICF signature, demographic information, and the reason for screen failure. No additional information will be required for subjects who fail screening.
- For consented subjects who meet eligibility criteria, all required screening information will be transcribed onto the appropriate page of the eCRF.

4.2 Treatment Phase

The treatment phase consists of eight weeks with seven visits for subjects in Arm B and 13 visits for subjects in Arms A which will be performed according to the following time schedule:

	First Cycle													
VISIT NUMBER	1[1]	1G[2]	2	2G	3	3G	4	5	5G	6	6G	7	7G	8[3]/ EOT
Week	1	1	2	2	3	3	4	5	5	6	6	7	7	8
Day	1	4	8	11	15	18	22	29	32	36	39	43	46	53
Arm A	X	X	X	X	X	X		X	X	X	X	X	X	
Arm B		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

However, in case of any non-hematological or hematological toxicities requiring postponement of the infusion, the subject may have up to four additional visits at 1-

week intervals between the regular visits. In case a further postponement will be necessary after the fourth additional visit, the subject has to be withdrawn from active study treatment. In addition, the subject has to be withdrawn from active study treatment in case the total treatment time will exceed 26 weeks [from Visit 1 (Arm A) or Visit 1G (Arm B)].

4.2.1 Treatment Visit 1 (Baseline for Arm A)

This visit applies to subjects in Arm A only and will be performed ≤ 7 working days after randomization.

At Treatment Visit 1 the following examinations and assessments have to be done prior to treatment:

- Any change in concomitant medication since last visit
- Blood samples for immediate laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry
    - Coagulation parameters

***Note**: Assessments of laboratory parameters performed 1 day prior to treatment is acceptable.*

- PK blood sample collection (within 3 hours prior to EndoTAG-1 treatment (predose), at the end of EndoTAG-1 i.v. infusion, and at 30 min, 1 hr, 2 hr, 4 hr and 6 hr post infusion) for first 50 subjects assigned to Arm A.
- Physical examination, including evaluation of all body systems
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal), and weight
- After all necessary exams have been finished the subject receives:
    - EndoTAG-1 infusion
- Assessment of Adverse Events (AE) (performed post treatment)

4.2.2 Treatment Visit 1G (Baseline for Arm B)

These visits apply to subjects in all study arms (A and B). Visit 1 G is the baseline visit for subjects in Arm B.

At Treatment Visit 1G the following examinations and assessments have to be done prior to treatment:

- Any change in concomitant medication since last visit

- Adverse events and serious adverse events occurring since last visit (for Arm A only)

  Note: *Assessment of Adverse Events will be performed post treatment for subjects assigned to Arm B*

- Blood samples for immediate laboratory analyses:
  - Hematology including differential hemogram
  - Clinical chemistry
  - Coagulation parameters

***Note**: Assessments of laboratory parameters performed 1 day prior to treatment is acceptable.*

- PK blood sample collection (within 3 hours prior to EndoTAG-1 treatment (predose) [only for first 50 subjects assigned to Arm A].
- Physical examination, including evaluation of all body systems (for Arm B only)
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal), and weight
- After all necessary exams have been finished the subject receives:
  - EndoTAG-1 infusion (Arm A)
- After all necessary exams have been finished the subject receives:
  - gemcitabine infusion (Arm A and B)

  Note: *For subjects in Arm A, EndoTAG-1 administration precedes the administration of gemcitabine.*
- Assessment of Adverse Events (AE) (performed post treatment for subjects assigned to Arm B)

4.2.3 Treatment Visits 2, 3, 5, 6 and 7

These visits apply to subjects in Arm A only.

At each of these visits the following examinations and assessments have to be done prior to treatment:

- Any change in concomitant medication since last visit
- Adverse events and serious adverse events occurring since last visit
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal) and weight. For measurement of body temperature, the same type of measurement is to be used throughout the study.

- Blood samples for immediate laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry [only at Treatment Visit 5 (Day 29)]

***Note**: Assessments of laboratory parameters performed 1 day prior to treatment is acceptable.*

- PK blood sample collection (within 3 hours prior to EndoTAG-1 treatment (predose)[only at Treatment Visits 2 (Day 8), 3 (Day 15), 5 (Day 29) and 7 (Day 43)] for first 50 subjects assigned to Arm A.
- After all necessary exams have been finished the subject receives:
    - EndoTAG-1 infusion

4.2.4 Treatment Visits 2G, 3G, 5G, 6G and 7G

These visits apply to subjects in all study arms (A and B).

At each of these visits the following examinations and assessments have to be done prior to treatment:

- Any change in concomitant medication since last visit
- Adverse events and serious adverse events occurring since last visit
- Blood samples for immediate laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry [only at Treatment Visit 5G (Day 32)]
    - Coagulation parameters

***Note**: Assessments of laboratory parameters performed 1 day prior to treatment is acceptable.*

- Physical examination, including evaluation of all body systems
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal) and weight. For measurement of body temperature, the same type of measurement is to be used throughout the study
- Depending on the results of the blood analyses subjects in Arm A receive after all necessary exams have been finished:
    - EndoTAG-1 infusion
- Depending on the results of the blood analyses subjects in all Arms (A and B) receive after all necessary exams have been finished:

- gemcitabine infusion

Note: *For subjects in Arm A, EndoTAG-1 administration precedes the administration of gemcitabine*

4.2.5 Treatment Visit 8 / End of Treatment (EOT) Visit

For all subjects the end of study treatment will be performed on day 53, 7 days after Visit 7G or when anyone of the criteria for early termination of study treatment is reached.

At this visit the following examinations and assessments have to be done:

- Any change in concomitant medication since last visit
- Adverse events and serious adverse events occurring since last visit
- Physical examination, including evaluation of all body systems
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal) and weight. For measurement of body temperature, the same type of measurement is to be used throughout the study
- Performance status (ECOG Performance Status)
- Blood samples for laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry
    - Tumor marker CA19-9
    - Urinalysis
    - Pregnancy test, if female of childbearing potential (serum or urine)
- Tumor imaging: Abdominal CT-scan with i.v. and gastrointestinal contrasts (or MRI), and chest X-ray (or CT or MRI). Thoracic CT- or MRI-scans have to be done additionally, if target lesions detected by chest X-ray are not clearly defined or not surrounded by aerated lung. Further imaging exams to be done if lesions are suspected in other areas.
- Evaluation of detected lesions according RECIST (version 1.1; *Eisenhauer et al*. 2009)
- Electrocardiogram

- Quality of Life Questionnaires (EORTC QLQ-C30 and EORTC PAN-26)

4.2.6 Continuation of Treatment, Subsequent Cycles

All subjects with complete/partial response or stable disease at Treatment Visit 8/End of Treatment visit who decide to continue study drug treatment will receive infusions according to the schedule performed during the study (EndoTAG-1 bi-weekly on days 1 and 4; gemcitabine on Day 4), starting within one week of the Treatment Visit 8/End of Treatment visit.

	Subsequent Cycles													
VISIT NUMBER	1[1]	1G[2]	2	2G	3	3G	4	5	5G	6	6G	7	7G	8[3]/EOT
Week	1	1	2	2	3	3	4	5	5	6	6	7	7	8
Day	1	4	8	11	15	18	22	29	32	36	39	43	46	53
Arm A	X	X	X	X	X	X		X	X	X	X	X	X	
Arm B		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

4.2.6.1 Subsequent Cycles, Treatment Visits 1, 2, 3, 5, 6 and 7

These visits apply to subjects in Arm A only.

At each of these visits the following examinations and assessments have to be done prior to treatment:

- Any change in concomitant medication since last visit
- Adverse events and serious adverse events occurring since last visit
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal) and weight. For measurement of body temperature, the same type of measurement is to be used throughout the study.
- Blood samples for immediate laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry [only at Treatment Visit 1 (Day 1) and Treatment Visit 5 (Day 29)]
- After all necessary exams have been finished the subject receives:
    - EndoTAG-1 infusion

4.2.6.2 Subsequent Cycles, Treatment Visits 1G, 2G, 3G, 5G, 6G and 7G

These visits apply to subjects in all study arms (A and B).

At each of these visits the following examinations and assessments have to be done prior to treatment:

- Any change in concomitant medication since last visit
- Adverse events and serious adverse events occurring since last visit
- Blood samples for immediate laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry [only at Treatment Visit 1G (Day 4) and Treatment Visit 5G (Day 32)]
    - Coagulation parameters
- Physical examination, including evaluation of all body systems
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal) and weight. For measurement of body temperature, the same type of measurement is to be used throughout the study
- Depending on the results of the blood analyses subjects in Arm A receive after all necessary exams have been finished:
    - EndoTAG-1 infusion
- Depending on the results of the blood analyses subjects in all Arms (A and B) receive after all necessary exams have been finished:
    - gemcitabine infusion

    Note: *For subjects in Arm A, EndoTAG-1 administration precedes the administration of gemcitabine*

4.2.6.3 Subsequent Cycles, Treatment Visit 8

These visits apply to subjects in all study arms (A and B). After each 7 weeks of continuation of treatment, the subject will attend Treatment Visit 8. These visits will be performed in 8-week intervals from the First Cycle, Treatment Visit 8.

At this visit the following examinations and assessments have to be done:

- Any change in concomitant medication since last visit
- Adverse events and serious adverse events occurring since last visit
- Physical examination, including evaluation of all body systems

- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal) and weight. For measurement of body temperature, the same type of measurement is to be used throughout the study
- Performance status (ECOG Performance Status)
- Blood samples for laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry
    - Tumor marker CA19-9
    - Urinalysis
    - Pregnancy test, if female of childbearing potential (serum or urine)
- Tumor imaging: Abdominal CT-scan with i.v. and gastrointestinal contrasts (or MRI), and chest X-ray (or CT or MRI). Thoracic CT- or MRI-scans have to be done additionally, if target lesions detected by chest X-ray are not clearly defined or not surrounded by aerated lung. Further imaging exams to be done if lesions are suspected in other areas.
- Evaluation of detected lesions according RECIST (version 1.1; *Eisenhauer et al*. 2009)
- Electrocardiogram
- Quality of Life Questionnaires (EORTC QLQ-C30 and EORTC PAN-26)

If the subject does not show progressive disease, subsequent treatment cycles can be started. Study treatment can be continued until progressive disease (according to RECIST) is documented.

During the continuation of treatment, the administration of study drug will not be postponed; if the subject experiences toxicities that prevent the administration of drug, the dose will be omitted.

4.3 Follow-Up Phase

All treated subjects will enter the Follow-Up Phase. The follow-up visits will be performed every eight weeks starting from the last study visit until the end of study or until death is reported.

Subjects who drop out of the study before receiving study medication will not be followed up.

4.3.1 Follow-Up Visit 1 (8 weeks after last study treatment)

At this visit the following examinations and assessments have to be done:

- Any change in concomitant medication since last visit

- Adverse events and serious adverse events occurring since last visit
- Physical examination, including evaluation of all body systems
- Vital signs, including blood pressure (supine), heart rate, and body temperature (oral, axillary, tympanic or rectal) and weight. For measurement of body temperature, the same type of measurement is to be used throughout the study
- Performance status (ECOG Performance Status)
- Blood samples for laboratory analyses:
    - Hematology including differential hemogram
    - Clinical chemistry
    - Coagulation parameters
    - Tumor marker CA19-9
    - Urinalysis
    - Pregnancy test, if female of childbearing potential (serum or urine)
- Tumor imaging: Abdominal CT-scan with i.v. and gastrointestinal contrasts (or MRI), and chest X-ray (or CT or MRI). Thoracic CT- or MRI-scans have to be done additionally, if target lesions detected by chest X-ray are not clearly defined or not surrounded by aerated lung. Further imaging exams to be done if lesions are suspected in other areas.
- Evaluation of detected lesions according RECIST (version 1.1; *Eisenhauer et al*. 2009)

  Note: *Only for subjects with tumor status other than progressive disease at the End of Treatment visit.*
- Electrocardiogram
- Quality of Life Questionnaires (EORTC QLQ-C30 and EORTC PAN-26)

4.3.2 Subsequent Follow-Up Visits

At these subsequent follow-up visits (at clinic or over the phone) the investigator will request the following information:

- Any change in concomitant medication since last visit / phone follow-up that was given due to an adverse event assessed as related to EndoTAG-1
- Adverse events and serious adverse events occurring since last visit / phone follow-up assessed as related to EndoTAG-1
- Any change in therapy for the pancreatic adenocarcinoma
- Survival status / death

4.4 Unscheduled Visits

In the event that the subject returns to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator.

5 Subject completion and withdrawal

5.1 Subject Completion

- A subject who completes at least the 48-week Follow-Up period after end (or discontinuation) of treatment, regardless of tumor response, will be considered as having completed the study.

5.2 Withdrawal of Subject from Therapy or Assessment

A subject who enters the Treatment Phase but does not complete the study, as defined in Section 5.1, is considered to have prematurely withdrawn from the Study. All subjects have the right to withdraw at any point during treatment without prejudice to future care. It will be documented whether or not each subject completed the clinical study. If for any subject, study treatment or observations were discontinued, the reason(s) will be recorded.

The Investigator can discontinue a subject at any time if it is considered medically necessary.

In addition, subjects WILL be withdrawn from the study, in consultation with the Medical Monitor and the Investigator, if any of the following are met:

- Withdrawal of consent by subject
- A subject is significantly non-compliant with the requirements of the protocol.
- The investigator determines that it is in the best interest of the subject.
- Withdrawal by investigator due to safety or ethical concerns
- Postponement of any administration of study drug for more than four consecutive weeks (only applicable for initial treatment cycle)
- Initial treatment period (cycle) lasting longer than 26 weeks (6 months)
- A subject becomes pregnant

  Note: *The pregnancy will be followed to term for safety follow-up. Relevant safety information collected after the study has completed will be reported as supplemental information.*
- Discontinuation of study by Sponsor
- Any major surgery
- Chemotherapy

Premature withdrawal from the study MAY occur if, in consultation with the Medical Monitor and the Investigator, any of the following are met:

- A subject is treated with a prohibited medication
- Major protocol violation

5.2.1 Discontinuation of Study Treatment

If a subject discontinues treatment between two Treatment Visit-8, all assessments scheduled for the next Treatment Visit 8 should be performed.

Additionally, a pregnancy test should be performed when the subject discontinues treatment, independent of the reason for discontinuing.

5.2.2 Data Collected for Withdrawn Subjects

Subjects may withdraw from the study or discontinue study treatment at any time; however, SynCore Biotechnology is dedicated to minimizing missing data in this study. An excessive rate of withdrawals can render the study non-evaluable; therefore, unnecessary withdrawal of subjects should be avoided. However, subjects must be removed if a safety concern occurs which is regarded as clinically relevant by the investigator. Should a subject decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible.

All assessments scheduled for the End of Treatment visit have to be performed if a subject discontinues treatment before the End of Treatment visit. A subject prematurely ending active study treatment will enter the regular follow-up period.

If a subject discontinues during the follow-up period, he/she should come in for one final follow-up visit and every attempt should be made to collect survival data over the phone.

Investigators considering discontinuing study treatment should contact the medical monitor prior to such discontinuation. Subjects who have study treatment discontinued will continue to be followed, per protocol, whenever possible.

Subjects who have study treatment discontinued due to a serious adverse event will be followed until resolution or stabilization of the event.

In the event that a subject is withdrawn from the study at any time due to an adverse event or serious adverse event (SAE), the procedures stated in Section 8.2 or 8.4, respectively must be followed.

Every attempt should be made to collect follow-up information. The reason for withdrawal from the study will be recorded in the source documents and on the appropriate page of the eCRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one certified letter.

For any subject who is lost to follow-up, the study site may attempt to ascertain survival information via following accesses but not limited to public database search, newspaper, hospital closed patient account.

5.3 Screen Failures

A subject who has signed a consent form, has been assigned a screening number, but is not treated is classified as a screen failure. Subject number, demographics and reason for screen failure will be recorded.

If any of the screening assessments show a clinically relevant abnormal finding, in particular a significantly abnormal laboratory parameter, which is in contrast to the eligibility criteria and/or interferes with the requirements of the study in the opinion of the investigator, the patient will be classified as a screening failure, will not be randomized in the study. Nevertheless, the subject has the chance to be re-screened at a later time point.

However, if a subject is dropped out of the study after randomization, he/she is not allowed to be re-screened and enter the study anew.

6 Study Treatments

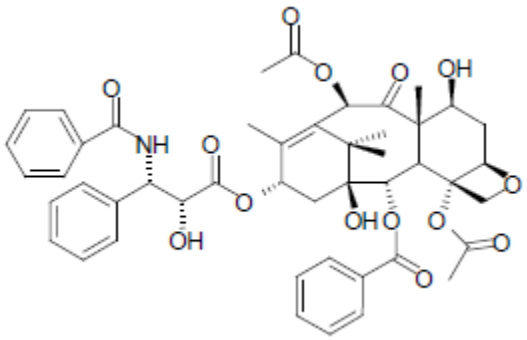
6.1 Investigational Product (IP): EndoTAG-1

The active pharmaceutical ingredient (API) in EndoTAG-1 is paclitaxel, which complies with the specifications of the European Pharmacopoeia (Ph.Eur.).

Recommended International Non-proprietary Name (INN): Paclitaxel

Compendial Name:	Paclitaxel (USP, Ph.Eur.)
CAS Registry Number:	[33069-62-4]
Molecular Weight:	853.9 g/mol
Formula:	$C_{47}H_{51}NO_{14}$

Figure 6-1: Structural Formula - EndoTAG-1 (paclitaxel)



EndoTAG-1 was first developed by Munich Biotech AG (Germany) under the names LipoPac and MBT-0206 and by Medigene AG under the name of EndoTAG-1. Since 2013, development and global commercialization of EndoTAG-1 is executed by SynCore Biotechnology Co., Ltd.

The Investigational Product (IP) is a powder for solution for infusion that appears as a white caked powder. It is reconstituted with water for injection prior to application. The resulting solution consists of small liposomal vesicles with an intensity weighted average particle size <300 nm.

The aqueous phase is a solution of trehalose and citric acid as stabilizer. Trehalose is a natural, non-reducing disaccharide at about iso-osmolal concentration (284 mosmol, 98 mg/mL), which needs to be taken into consideration when treating diabetic patients (insulin-dependent diabetes mellitus, IDDM). Citric acid is used at a concentration of 60 µM in solution in order to maintain a low pH and therefore to increase the chemical stability of the API in the liquid phase. The IP contains less than 0.5% (w/w) ethanol and has a pH of 3 to 5.

Table 6-1: Excipients of EndoTAG-1

Excipient:	Formula:	Molecular Weight:	Function:
DOTAP-Cl	$C_{42}H_{80}NO_4Cl$	698.55 g/mol	Membrane compound
DOPC	$C_{44}H_{84}NPO_8$	786.12 g/mol	Membrane compound
Trehalose dihydrate	$C_{12}H_{22}O_{11}•2H_2O$	378.3 g/mol	Cryoprotectant
Citric acid, anhydrous	$C_6H_8O_7$	192.12 g/mol	Stabilizing acidifier

6.2 Comparator Product (IP): Gemcitabine

Gemcitabine is used as a comparator with a marketing authorization (for pancreatic cancer at the dosage used in this protocol) in the respective countries. Further information on gemcitabine can be found in the Summary of Product Characteristics (SPC) of gemcitabine.

6.3 Packaging and Labeling of Investigational Product

EndoTAG-1 is packed in 100 mL glass vials (hydrolytic class I) with bromobutyl stoppers fixed by standard color coded aluminum flip off caps.

The Label information for the Primary Container (= immediate packaging) and Secondary Container (= outer packaging) will comply with the requirements of GMP Annex 13. If applicable, local labels will be further supplemented by further terms if requested by local law in the participating country.

The label will contain the following information:

Manufacturer: SynCore Biotechnology 4F, No. 69, DongXing Rd., XinYi Dist., Taipei City 110, Taiwan, Tel.: +886-2-27603688
EndoTAG-1: 6.4 mg
Batch-Numbers.:
Powder for solution for infusion
1 vial contains 2.63 g lyophilised powder containing 6.40 mg liposomal paclitaxel
For i.v. application after reconstitution
Trial reference code: CT 4006
For clinical trial use only
Vial-No.:
Store at 2-8°C, protected from light
Handle and discard as required for cytotoxic drugs
CAUTION: New drug - limited by United States law to Investigational Use (only for USA)

6.4 EndoTAG-1: Dose Justification

Preclinical safety data obtained so far justify multiple administrations of EndoTAG-1 up to a dose of 44 mg/m^2 lipid complexed paclitaxel to patients. EndoTAG-1 has been investigated in several clinical studies and a favorable safety profile without major safety concerns at a dose of 44 mg/m^2 lipid complexed paclitaxel has been assessed. Because of this and because of the complementary anti-neovascular mode of action of EndoTAG-1, it is expected that there is no interference in respect to safety and tolerability between EndoTAG-1 and gemcitabine.

However, due to the targeting mode of action of EndoTAG-1 lower doses might be as effective as higher doses with probably less side effects, especially when combined with standard chemotherapy. This assumption was confirmed with an exploratory analyses of CT 4001 study (*A Controlled, Randomized, Open label Phase II Trial to Evaluate Safety and Efficacy of a 1st line Combination Treatment with Weekly Infusion of Gemcitabine and Twice Weekly Administration of Lipid Complexed Paclitaxel (EndoTAG-1) in Three Dose Levels Compared with Gemcitabine Monotherapy in Patients with Measurable Locally Advanced and/or Metastatic Adenocarcinoma of the Pancreas*) with focus on a subpopulation of subjects with baseline ECOG grade of 0 and 1. The results from the analyses demonstrated that hazard ratios (for PFS and OS) favor combination therapy of gemcitabine plus the EndoTAG-1 (for all three doses; 11 mg/m², 22 mg/m² and 44 mg/m²) when compared to the gemcitabine monotherapy. However statistically significant differences were observed for the two endpoints (OS and PFS) between the gemcitabine monotherapy and EndoTAG-1 (22 mg/m²) plus gemcitabine.

Based on the results of exploratory analyses of CT 4001 study, EndoTAG-1 (22 mg/m² lipid complexed paclitaxel) dose is selected for this Phase 3 study.

6.5 Study Dosing Schedule

Arm A:

- Treatment cycle 1: EndoTAG-1 will be given at a dose of 22 mg/m^2 as an intravenous infusion which should be started slowly and increased to a maximum of 1.5 ml/min (15 min at 0.5 ml/min, 15 min at 1.0 ml/min. and thereafter 1.5 ml/min.) on days 1, 4, 8, 11, 15, 18, 29, 32, 36, 39, 43 and 46 plus gemcitabine 1000 mg/m², 30 min. i.v. infusion on days 4, 11, 18, 32, 39, and 46 of cycle 1 until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent
- Subsequent treatment cycles: EndoTAG-1 on days 1, 4, 8, 11, 15, 18, 29, 32, 36, 39, 43 and 46 plus gemcitabine on days 4, 11, 18, 32, 39, and 46 of all subsequent cycles, until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent

Arm B:

- Treatment cycle 1: gemcitabine 1000 mg/m², 30 min. i.v. infusion on days 4, 11, 18, 32, 39, and 46 of cycle 1 until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent
- Subsequent treatment cycles: gemcitabine on days 4, 11, 18, 32, 39, and 46 of all subsequent cycles, until any one of the following occurs: progressive disease or unacceptable toxicity or withdrawal of consent

6.6 Dispensing, Storage and Accountability

6.6.1 Preparation of EndoTAG-1 and i.v. administration

EndoTAG-1 is delivered to the hospital pharmacy as a sterile, white powder for infusion (Lyophilisate) packaged in glass vials for single use. Until administration to the subject the investigational medicinal product has to be stored at 2-8°C, protected from light. The hospital pharmacy has to take care of the disposal of used vials and materials in contact with the study medication in compliance to the local regulations concerning hazardous (cytotoxic) waste.

The stability of the reconstituted drug in the vial as the primary container system is 24 hours when stored at 25°C ± 2°C.

Prior to application, EndoTAG-1 has to be reconstituted with water for injection under aseptic conditions using a safety work bench for cytostatics or similar safety measures at the pharmacy. After transfer of the reconstituted drug to the infusion system, it is stable for a maximum of 4 hours.

The solution is allowed to rest undisturbed at 2-8°C to allow complete reconstitution. The required application volume is calculated from the subject's body weight and the dose schedule. A sufficient number of reconstituted vials have to be prepared to cover the application volume. For large application volumes, the preparation is split into portions, which can be used one after the other and stored at 2-8°C until needed. The maximum volume for one portion should not exceed 200 ml to allow the administration within the time frame of 4 hours and ensure in-use stability throughout the application. The maximum infusion rate must not exceed 90 mL/hour = 1.5 mL/min and at the beginning of intravenous infusion the rate should be accelerated slowly from 0.5 mL/min to 1.5 mL/min over a period of 30 min. The investigational medicinal product must not be stored and used a second time.

After randomization and before start of treatment phase it can be considered to apply a central venous catheter to the subjects (if not already present) to facilitate administration of study medication.

The investigator or pharmacist must maintain accurate records of the receipt of all investigational medicinal product provided by the sponsor, including date received, batch number, expiration date, subject number, amount received and disposition (dispensation date, amount of investigational medicinal product dispensed and subject identification number).

All remaining unused investigational medicinal product has to be returned to the supplier after study termination or destroyed at the site's pharmacy after the written permission of the sponsor according to standard operating procedures. Destruction of investigational medicinal product has to be documented by the investigator and/or pharmacist. The respective documentation has to be sent to the Sponsor.

The pharmacist and the investigator have to follow the detailed information on preparation and administration of EndoTAG-1 provided by the sponsor in a separate document.

6.6.2 Preparation of gemcitabine and i.v. administration

The investigational sites have to buy the gemcitabine supply locally. Associated costs will be reimbursed by the sponsor.

For reconstitution of the lyophilized gemcitabine please follow these instructions:

- Calculate the amount of gemcitabine needed for administration of 1000 mg/m^2.
- To reconstitute, add 25 ml of 0.9% Sodium Chloride Injection to each required 1g vial or 5 ml of 0.9% Sodium Chloride Injection to each required 200 mg vial.
- Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/ml. The total volume upon reconstitution will be 5.26 ml or 26.3 ml, respectively.
- Complete withdrawal of the vial contents will provide 200 mg or 1g of gemcitabine, respectively.
- Check that the solution is free from visible particles and that it is clear and colorless to light straw-colored.
- Transfer the appropriate amount of reconstituted gemcitabine to an infusion bag. The drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/ml.
- Administer the gemcitabine solution as an intravenous infusion over a period of 30 minutes.
- Chemical and physical in-use stability of gemcitabine solution has been demonstrated for 24 hours at 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature. Gemcitabine solution must not be stored cold, as precipitation may occur.

6.7 Dose adjustments

At the visit of a first infusion (Arm A: Visit 1, Arm B: Visit 1G), the subject has to receive 100% of the trial medication (Arm A: EndoTAG-1 and gemcitabine; Arm B: gemcitabine). If, for any reason it is clear that the subject will not be able to receive the full dose of trial medication at the first infusion, the treatment should not be initiated and the subject should be immediately withdrawn from the study.

Important: For the purpose of dose adjustments due to clinical chemistry results (non-hematological toxicity) only basic parameters that can be analyzed without

longer waiting times (so called "emergency lab values") will be considered. These values are: AST, ALT and creatinine. The remainder of clinical chemistry will be assessed for safety issues, but not considered for the decision of dose adjustment.

In case of hematological, non-hematological and special hematological toxicities, treatment might be reduced or postponed (during continuation of treatment: reduced or omitted) as specified in the following. In case of postponement, all examinations of the respective visit will be repeated one week later and study medication will be administered according to the specifications given in Section 6.7.1 and 6.7.2.

6.7.1 Dose Modifications for EndoTAG-1

Criteria for Dose Modifications

- Grade 4 neutropenia lasting 7 or more days
- Febrile neutropenia
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with significant bleeding or requiring transfusion
- Grade ≥ 3 stomatitis/vomiting/diarrhea
- Other ≥ Grade 3 and 4 toxicities [a, b]

[a] *Except Grade 3 fatigue/asthenia or transient arthralgia/myalgia for which no dose modification is required.*

[b] *To be adjusted as medically indicated after discussion between Investigator and Sponsor*

If any of the above mentioned toxicity criteria are present, no study medication is to be administered at this visit. If the toxicity criteria are no longer fulfilled at the next scheduled visit, EndoTAG-1 is to be administered at a reduced dose of 11 mg/m². If the subject tolerates treatment at the reduced dose (i.e. does not develop any of the above mentioned toxicities), the EndoTAG-1 dose should be re-escalated to 22 mg/m². If re-escalation is not tolerated by the subject, the dose is to be permanently reduced to 11 mg/m². The attempt for re-escalation of the EndoTAG-1 dose is to be made only once throughout the study. Subjects not tolerating treatment even after dose reduction will be taken off study.

6.7.2 Dose Modifications for Gemcitabine

6.7.2.1 Dose Modifications for Hematologic Adverse Reactions

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥ 1000	And	≥100,000	100%
500-999	Or	50,000 – 99,999	75%
<500	Or	<50,000	Hold

6.7.2.2 Dose Modifications for Non-Hematologic Adverse Reactions

Permanently discontinue Gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Note: Withhold gemcitabine or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

If a subject fails to meet criteria for retreatment on the day the next treatment is scheduled, treatment should be omitted and the subject will be re-evaluated at least weekly. Treatment may be omitted for a maximum of 2 weeks. If treatment is omitted for >1 week, a new cycle should be started upon continuation of treatment. Any subject who fails to recover from a treatment related adverse event to baseline or Grade 2 within 2 weeks of scheduled retreatment will be withdrawn from the study with the exception of subjects who benefit from study treatment (non-progressive disease according to RECIST v.1.1), who may continue treatment on study after consultation and approval of the Sponsor.

6.7.3 Dose Modification for Subjects Assigned to Arm A (EndoTAG-1 plus Gemcitabine)

Subjects may start a new cycle of combination therapy if ANC is > 1,500/mm^3, platelets are >100,000/mm^3 and treatment-related non-hematologic adverse event including neuropathy has resolved to baseline or Grade 2. Subjects with Grade 2 neuropathy will not be retreated until resolved to Grade 1.

Note: Subjects on treatment arm A who requires discontinuation of gemcitabine will not continue on single-agent EndoTAG-1 alone. However, subjects in Treatment Arm A who require discontinuation of EndoTAG-1 due to toxicity may continue on gemcitabine monotherapy. Subjects on Arm B (gemcitabine alone) will not be offered treatment with EndoTAG-1 at the time of discontinuation (no cross-over allowed).

6.8 Contraindications, Precautions, and Warnings for EndoTAG-1

6.8.1 Contraindications

EndoTAG-1 is contraindicated in patients with known severe hypersensitivity to paclitaxel or to any excipients.

EndoTAG-1 should not be used in patients with baseline neutrophils < 1,000/mm^3.

There is no experience of the use of EndoTAG-1 in pregnant women. Like other cytotoxic anticancer drugs, EndoTAG-1 could cause fetal harm when administered to a pregnant woman and, therefore, is contraindicated during pregnancy. Women of childbearing potential must be advised to avoid pregnancy while they or their male partner are receiving EndoTAG-1 and in the 90 days following discontinuation of EndoTAG-1 therapy. Should they become pregnant after all, they should inform the treating doctor immediately.

It is not known whether EndoTAG-1 is excreted in human milk. EndoTAG-1 is contraindicated in nursing mothers. It is recommended that nursing be discontinued when receiving EndoTAG-1 therapy.

6.8.2 Precautions and Warnings

Sometimes infusion associated reactions may occur within minutes of starting the infusion of EndoTAG-1. These are characterized by symptoms including dyspnea, flushing, chest pain, hypertension, tachycardia, sweating, shortness of breath, chills, back pain, tightness in chest and throat as well as hypotension. Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medication to treat these symptoms (e.g. antihistamines, corticosteroids, catecholamines, see below) as well as emergency equipment should be available for immediate use. In most patients' treatment can be resumed after all symptoms have resolved, without recurrence. To minimize the risk of infusion reactions, the infusion has to be started slowly and infusion rate should not exceed 1.5ml/min. The patient should be carefully monitored during infusion.

Please follow the local procedures for handling of cytotoxic drugs.

EndoTAG-1 contains the cytotoxic drug paclitaxel and, as with other potentially toxic compounds, caution should be exercised in handling EndoTAG-1. The use of gloves is recommended. If EndoTAG-1 solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If EndoTAG-1 contacts mucous membranes, the membranes should be flushed immediately and thoroughly with water.

Any unused product and all equipment used for the preparation and administration of EndoTAG-1 or contacting EndoTAG-1 must be disposed of in accordance with local requirements concerning cytotoxic drug products.

6.8.3 Emergency Medication for infusion related toxicity

- H2-receptor antagonist (e.g. cimetidine 300 mg i.v. or ranitidine 50 mg i.v.)
- H1-antihistaminic (e.g. clemastine 2mg i.v.)

together with other "state-of-the-art" emergency medications (e.g. corticoids, catecholamines) have to be kept handy on site.

6.9 Contraindications, Precautions, and Warnings for Gemcitabine

For contraindications, precautions, and warnings, refer to SPC of gemcitabine in details.

Concomitant radiotherapy

Concomitant radiotherapy (given together or ≤7 days apart): Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Details and recommendations for use can refer to SPC of gemcitabine.

Live vaccinations

Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

Fertility

Men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine.

6.10 Other study medication

No other study medication is allowed while the subject is participating in the trial.

6.11 Prior and Concomitant Medication

6.11.1 Prior Treatment

Patients are not allowed to have received any chemotherapeutical treatment (except FOLFIRINOX as the first-line therapy) for pancreatic adenocarcinoma prior to enrollment.

6.11.2 Permitted Treatment

Premedication:

In arm A group, Dexamethasone and anti-histamine drugs such as diphenhydramine (or its equivalent), cimetidine or ranitidine may be given as premedication for EndoTAG-1 (liposomal paclitaxel).

Paclitaxel-induced nausea and vomiting may be prevented by i.v. application of ondansetron (8 mg), granisetron (3 mg), tropisetron (4 mg) or dolasetron (100 mg) given 30 min prior to chemotherapy. Delayed nausea and vomiting may be treated with oral metoclopramide and dexamethasone.

G-CSF or GM-CSF:

In case of observed severe hematotoxicity (i.e., maximal hematotoxicity with granulocytes < 0.5/µl or granulocytes < 1.0/ µl possibly accompanied by fever> 38.5° C, or hematotoxicity necessitating treatment delay), colony-stimulating factors should be given prophylactically starting on day 2 of the following cycles until recovery to prevent further episodes of hematotoxicity.

Note: The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

7 Description of Study Assessments and Procedures

7.1 Informed Consent

Written informed consent will be obtained for this study by the Investigator or designee from all subjects before the performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and must adhere to Good Clinical Practice (GCP). The Investigator, or designee, must fully inform subjects of all pertinent aspects of the study. Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the trial. All questions about the trial must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

7.2 Assessment of Eligibility

During the Screening Phase and prior to treatment administration, the Investigator must assess a subject's continued suitability and eligibility for the trial. The Inclusion and Exclusion criteria of this Protocol are described in Sections 3.4.1 and 3.4.2. If the subject is not suitable or eligible for the trial then the subject will be a screen failure.

7.3 Disease History

Disease history will be assessed at screening and will include the following:

1. Date of first diagnosis and the history of the course of the disease
2. Histologically or cytologically confirmed adenocarcinoma of the pancreas
3. At least one measurable tumor lesion according to RECIST version 1.1 as assessed by the investigator (local radiological image assessment).
4. Details of the prior chemotherapy, surgical or radiation therapy.

7.4 Medical History

Medical history will be assessed at screening and will include the following:

- Medical and surgical history, including past or concurrent clinically significant disease(s), or symptoms experienced during 30 days prior to screening are to be recorded, using the body system categories outlined below. For each history, the specific medical terminology for the disease/disorder/condition, the date of diagnosis, and the history status (resolved or ongoing) will be documented.

Cardiovascular	Lymphatic
Respiratory	Hematologic
Gastrointestinal	Immunologic
Renal	Dermatologic
Hepatic	Psychiatric
Neurological	Genitourinary
Endocrine	Other

7.5 Demographic Information

For the purposes of this study, demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

7.6 ECOG Performance Status

The ECOG performance status will be documented at screening and at all Treatment Visit 8/End of Treatment visit.

Table 7-1: ECOG Performance Status Scale[1]

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

[1] (Oken, Martin M., et al. 1982)

5	Dead.

7.7 Physical Examination

A complete physical examination will be performed to include a review of all systems. Each body system will be classified as being either normal or abnormal, with abnormalities for each body system noted. Subsequent physical examinations will identify changes from the baseline examination with both positive and negative changes being noted.

The complete physical examination will include routine examinations for the following:

- General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Lymph Nodes
- Heart/Cardiovascular abnormalities
- Respiratory
- Abdomen
- Genitourinary
- Musculoskeletal and Extremities
- Neurologic abnormalities Dermatologic abnormalities
- Any other body system for which an abnormality is noted and which, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject; i.e., the abnormality is clinically significant (CS).

7.8 BSA Calculation

BSA will be calculated on dosing days, using the formula (Mosteller, 1987) below:

$$BSA\ (m^2) = [Height\ (cm) \times Body\ Weight\ (kg)/3600]^{1/2}$$

The total dose (mg) will be calculated as:

$$Total\ Dose\ 1/Dose\ 2\ (mg/m^2) \times BSA\ (m^2)$$

7.9 Vital Signs

Vital signs, including

- Height (cm) (only performed at screening)
- Weight (kg) at each visit before a study treatment infusion
- Blood pressure (supine),
- Heart rate, and
- Body temperature (oral, axillary, tympanic or rectal)

For measurement of body temperature, the same type of measurement is to be used throughout the study

7.10 Laboratory Assessments

The local laboratory for the study site will be used and all procedures will be performed following the standard operating procedure (SOP) of the local laboratory.

The parameters assessed are detailed below:

Hematology

Hemoglobin, Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), RBC count, WBC count, WBC Differential, Absolute neutrophil count and Platelet count

Clinical Chemistry

Total Bilirubin, Alkaline Phosphatase, ALT, AST, Gamma-glutamyl transferase (GGT), Albumin, Total Protein, Creatinine, Urea (BUN), Uric acid, Sodium, Potassium, Calcium, Chloride, Glucose and Triglycerides (TG).

Coagulation

INR, PT, aPTT, total Fibrinogen

Urinalysis

pH, Appearance, Color, Specific gravity, Viscosity, Turbidity, Ketones, Bilirubin, Blood, Glucose, Protein, Nitrites, Urobilinogen, Leukocyte esterases, Microscopic exam includes bacteria, cast, crystals, epithelial cells, RBC, and WBC.

Pregnancy test

A urine or serum pregnancy test for women of childbearing potential

Tumor Marker

CA 19-9

7.11 PK Blood Sample Collection

PK sample collection will only be performed from first 50 enrolled subjects assigned to Arm A.

- Pharmacokinetic sampling on Day 1: C_{max}, t_{max}, $t_{½}$ term, V_D, and CL for paclitaxel, 6α-OHpaclitaxel and DOTAP within 3 hours prior to EndoTAG-1 treatment (predose), at the end of EndoTAG-1 i.v. infusion, and at 30 min, 1 hr, 2 hr, 4 hr and 6 hr post infusion.
- Pharmacokinetic sampling on Days 4, 8, 15, 29 and 43: trough levels of paclitaxel, 6α-OH-paclitaxel and DOTAP within 3 hours prior to EndoTAG-1 treatment (predose).

7.12 Quality of Life Questionnaire

The EORTC-QLQ-C30 [European Organization for Research and Treatment of Cancer Quality of Life Questionnaire], and PAN-26 module, which was specifically developed for clinical trials in pancreatic cancer, will be used to evaluate clinical benefit.

7.13 Tumor Imaging

Abdominal CT-scan with i.v. and gastrointestinal contrasts (or MRI), and chest X-ray (or CT or MRI). Thoracic CT- or MRI-scans have to be done additionally, if target lesions detected by chest X-ray are not clearly defined or not surrounded by aerated lung. Further imaging exams to be done if lesions are suspected in other areas.

7.14 Tumor Response Evaluation

7.14.1 Definition of lesions

Tumor response will be assessed according to the RECIST (version 1.1; *Eisenhauer et al*. 2009). At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

7.14.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5mm).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

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

7.14.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

7.14.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

7.14.2 Method of Assessment

The same method of assessment and the same technique have to be used to characterize each identified and reported lesion at screening, at end of treatment and during follow-up.

Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes).

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI should be performed with contiguous cuts of 5 mm or less in slice thickness, if possible [minimum measurable lesion size: long axis ≥ 10 mm (CT + MRI) and 2 x slice thickness, if the slice thickness is > 5 mm].

Ultrasound may only be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules.

7.14.3 Baseline documentation of 'target' and 'non-target' lesions

Only subjects with measurable disease at baseline should be enrolled in this study. For evaluation of tumor response, lesions present at screening will be separated into target and non-target lesions according to the following criteria:

Target Lesions:

- A maximum of five (5) target lesions in total (up to two (2) per organ)
- Select largest reproducibly measurable lesions. If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be measured
- Add up longest diameters (LD) of non-nodal lesions (axial plane) and short axis diameters of nodes. This is the "sum of the longest diameters" (SLD)

Non-Target Lesions

- All other lesions present at screening. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")

7.14.4 Evaluation of target lesions

- Measure LD (axial plane) for each target lesion
- Measure short axis for target lymph nodes
- Add these measurements to get the SLD
- If too small to measure, a default value of 5 mm is assigned. If the lesion disappears completely, the measurement is recorded as 0 mm.
- Splitting or coalescent lesions
    - If a target lesion fragments into multiple smaller lesions, the LDs of all fragmented portions are added to the sum
    - If target lesions coalesce, the LD of the resulting coalescent lesion is added to the sum

Table 7-2: Target Lesion Evaluation

Response	Definition
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	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 if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

7.14.5 Evaluation of non-target lesions

Table 7-3: Non-Target Lesion Evaluation

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).

7.14.6 Evaluation of Best Overall Response

The best overall response is the best response recorded from start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

The following table provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions:

Table 7-4: Time point response: subjects with target (± non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

7.15 Electrocardiogram

A 12-lead ECG will be conducted at the Screening Visit (SV) and at all Treatment Visit 8/End of Treatment visit.

7.16 Concomitant Medication

To avoid the use of concomitantly administered CYP3A4 and CYP2C8 inhibitors and inducers (see paclitaxel package insert).

All medications and therapies administered or taken by the subject beginning 30 days prior to Screening Visit and throughout the study will be recorded in the source documents and, for randomized subjects, on the appropriate page of the electronic Case Report Form (eCRF). For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
    - **Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing
- Indication for use
- The start date

- The stop date (if medication/therapy is not ongoing)

7.17 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.

7.18 Study Treatment Administration

Refer to Section 6 for details.

7.19 Appropriateness of Measurements

The measurements used in this in study are considered appropriate for the indication studied. Disease response is a common tool used in cancer trials to study the effectiveness of the study drug. Safety and tolerability of the study drug will be reported during the trial.

8 Adverse Events Definitions and Reporting

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs as detailed in this Section of the protocol.

8.1 Adverse Events (AE)

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the medicinal product (definition per ICH E2A and E6 R1).

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology on the AE eCRF page. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

AEs will be elicited through direct questioning and subject reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

For all AEs, the Investigator must pursue and obtain information adequate to both determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see Section on SAEs) requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE.

Interventions for pre-treatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrolment are not considered AE.

Laboratory results, which are out of range at the screening assessment (up to 14 days prior to randomization) do not fulfill the definition of an AE since these results represent the baseline information.

Progression of the disease under investigation as well as an increase in CA19-9 values will not be regarded as adverse event during the course of this trial. Death due to disease progression has to be reported to the sponsor via the "Death due to Disease Progression" form.

8.1.1 Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the subject is no longer in the treatment phase of the protocol or died.

8.1.2 Intensity Assessment

The severity of the AE will be graded according to the NCI Common Terminology Criteria for AEs (CTCAE) Grading Scale Version 4.03 (Publish Date: June 14, 2010, http://ctep.cancer.gov/reporting/ctc.html).

The maximum severity (intensity) of the AE will be categorized by the Investigator as follows:

Table 8-1: CTCAE v4.03 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.‡

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
‡Unlike the AE outcome assessment (see section 8.1.5), a subject may have more than one Grade 5 event.

-Common Terminology Criteria for Adverse Events (CTCAE), v4.03: June 14, 2010

For AEs not covered by NCI CTCAE, the severity will be characterized as "mild," "moderate," or "severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities
- Severe events interrupt the subject's usual daily activities.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates). All AEs, due to any cause that occurs during the investigation, whether or not related to the study drug, should be reported to the Safety Coordinator.

8.1.3 Causality Assessment

The investigator will assign a relationship to the study drug (i.e. causality) for all AEs that occur during the study using the definitions below:

- **Unrelated:** The AE is clearly related to other causes such as participant's clinical state, environmental factors, or other therapies administered.
- **Unlikely to be related:** The AE does not follow a reasonable temporal sequence from study drug administration; could readily have been produced by other causes such as the participant's clinical state, environmental factors, or other therapies administered; does not follow a known response pattern to the study drug.
- **Possibly related:** The AE follows a reasonable temporal sequence from study drug administration; follows a known response pattern to the study drug; could readily have been produced by other causes such as the participant's clinical state, environmental factors, or other therapies administered.
- **Probably related:** The AE follows a reasonable temporal sequence from study drug administration; follows a known response pattern to the study drug; cannot be reasonably explained by other factors such as the participant's clinical state, environmental factors, or other therapies administered; improvement upon cessation of test drug.
- **Definitely related:** The AE follows a reasonable temporal sequence from study drug administration; follows a known response pattern to the study drug; cannot be reasonably explained by other factors such as the participant's clinical state, environmental factors, or other therapies administered; improvement upon cessation of test drug or reappears upon repeat exposure (if rechallenge occurs).

8.1.4 Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

8.1.5 Outcome Assessment

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

8.2 Adverse Event Reporting

All AEs occurring during the study (from the time of the first study treatment until 28 days after the last dose of study treatment) observed by the Investigator or reported by the subject (whether or not attributed to study drug), will be reported on the eCRF. Clinically significant AEs considered related or non-related to the IP by the Investigator

or the Sponsor will be followed until resolved or considered stable by the Investigator. The following information must be provided: description; dates of onset and resolution; severity; assessment of relatedness to IP; whether treatment was given as a result of the event and the outcome of the event. The investigator may be asked to provide follow-up information.

All AEs, serious or not, that result in the subject's permanent withdrawal of IP or from the study will be discussed between the investigator and medical monitor. The eCRF for EOT/Early Withdrawal Visit should be completed including reason of withdrawal.

It will be the investigator's clinical judgment whether or not an AE is of sufficient severity to require the subject's removal from study treatment. A subject may also voluntarily withdraw from study treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo EOT assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

8.3 Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that at any dose (ICH E2A and E6 R1):

- Results in death.
- Is life-threatening.
  This means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the Investigator's and the sponsor's assessment. If either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

All SAEs must be reported to the sponsor or sponsor designee immediately after the Investigator becomes aware of the event, along with a determination as to whether it is associated with the IP or any other study procedure.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the SAE definition.

8.4 Serious Adverse Event Reporting

All SAEs, irrespective of relationship to IP, must be reported within 24 hours of the Investigator knowledge of the event to Covance Patient Safety Services within 24 hours.

CRO Covance	Covance Patient Safety Services Email: SAEIntake@covance.com Fax: +1-888-887-8097 Phone: +61-2-88792000 (SAE hotline)

A written SAE reports must include a full description of the event as described in Section 8.1 The Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram [ECG] reports, discharge summary, hospital notes, etc, if applicable.

Relevant medical records should be provided to the Sponsor or CRO as soon as they become available; autopsy reports should be provided for deaths if available. Should an Investigator be made aware of an SAE occurring any time after the reporting period, it must be promptly reported.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the IP or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

8.5 SAE Follow-Up

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

8.6 Suspected Unexpected Serious Adverse Reactions (SUSAR)

Suspected Adverse Reaction (SAR)

Suspected adverse reaction means any adverse event or adverse experience for which there is a reasonable possibility that the IP caused the adverse event. Inherent in this definition, and in the requirement to report them, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Unexpected

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents.

8.7 Expedited Reporting of SUSAR

Sponsor (or designee) will provide written notification to the regulatory agencies i.e. FDA and all participating investigators of any suspected adverse reaction that is both serious and unexpected. Each notification should be submitted as specified below, depending on the type of event. Each written notification may be submitted on FDA form 3500A and/or CIOMS-I.

- 7-Day Expedited Report: any serious and unexpected suspected adverse reaction that is fatal or life-threatening will be reported as soon as possible and no later than 7 calendar days after the sponsor's (or designee's) initial receipt of the information.
- 15-Day Expedited Report: any serious and unexpected suspected adverse reaction that is not fatal or life-threatening will be reported as soon as possible and no later than 15 calendar days after the sponsor (or designee) determines that the event qualifies for reporting (21 CFR 312.32).

8.8 Pregnancies

All initial reports of pregnancy must be reported to the Sponsor within 24 hours of the Investigator knowledge of the event using the appropriate pregnancy form.

For IP, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed (e.g., environmental exposure) to the IP, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the IP (maternal exposure) for 28 days after last dose of or exposure to IP.
- A male partner of a pregnant female has been exposed to the IP, either due to treatment or environmental exposure, within 3 months prior to the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the IP or exposure as defined above, the Investigator must submit this information on a Pregnancy form to the Sponsor (or its designated representative). In addition, the Investigator must submit information regarding environmental exposure to an IP in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Pregnancy form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see following information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all exposure during pregnancy reports with an unknown outcome. The Investigator will follow the pregnancy until completion or until pregnancy termination (e.g., induced abortion) and then notify the Sponsor or its designated representative of the outcome as a follow-up to the initial Pregnancy form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [including that in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be

reported as SAEs when the Investigator assesses the neonatal death as related to exposure to IP.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9 Statistical Considerations

This section presents general information about statistical considerations and concepts such as randomization, stratification, statistical power, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document; i.e., the Statistical Analysis Plan (SAP).

9.1 Treatment Groups

The following treatment groups will be assessed:

Group	Description
Arm A	EndoTAG-1 22 mg/m^2 twice weekly plus gemcitabine 1000 mg/m^2 once weekly
Arm B	gemcitabine 1000 mg/m^2 once weekly

9.2 Description of Study Endpoints

9.2.1 Efficacy Endpoints

9.2.1.1 Primary Efficacy Endpoints

There are two primary endpoints for the study:

- 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.

9.2.1.2 Secondary Efficacy Endpoints

The secondary endpoints for the study are:

- Percentage of subjects with Objective Response (OR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1)
- *Percentage of subjects with objective response is based on assessment of complete response (CR) or partial response (PR) according to RECIST v.1.1.*
- Duration of Response (DR)
- *Duration of Response is defined as the time from the first documentation of objective tumor response (date of the first CR or PR) to objective tumor progression or death due to any cause.*
- Percentage of subjects with disease control according to RECIST v.1.1

- *Percentage of subjects with disease control is based on assessment of complete response (CR) or partial response (PR) or stable disease (SD) according to RECIST v.1.1*
- Serum Carcinoma Antigen 19-9 (CA 19-9) response rate
- *Responders are defined as subjects with a reduction in CA 19-9 levels by least 50% from baseline to the end of cycle 1 (or end of full treatment course).*

9.2.2 Safety Assessments

Safety will be assessed based on the following assessments:

- 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

9.2.3 Exploratory Endpoints

- Change From Baseline in European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ- C30) Score
  EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status (GHS), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0- 100 scale; higher score=better level of functioning or greater degree of symptoms. Change from baseline=Cycle/Day score minus baseline score.
- Change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Pancreatic 26 (EORTC QLQ- PAN26) Score
  QLQ-PAN26 consists of 26 questions (Qs) relating to disease symptoms, treatment (Tx) 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.

9.3 Sample Size Determination and Rationale

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 collect 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 the 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 disease progression 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 9-1, 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 9-2, 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 9-1: Overall Survival Sample Size Plot: Total sample size requirement vs. the median survival time (month) in the treatment arm A.

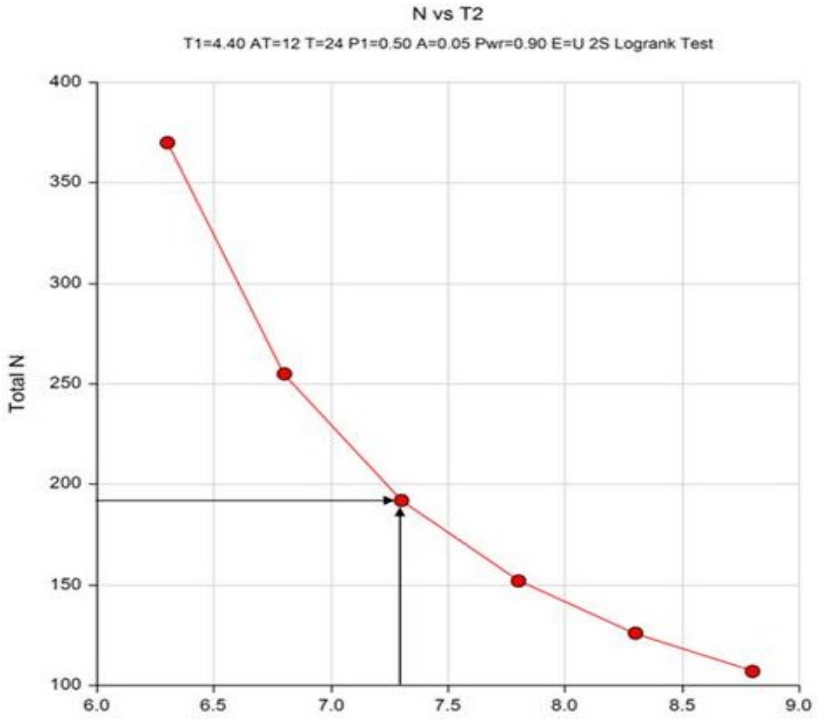
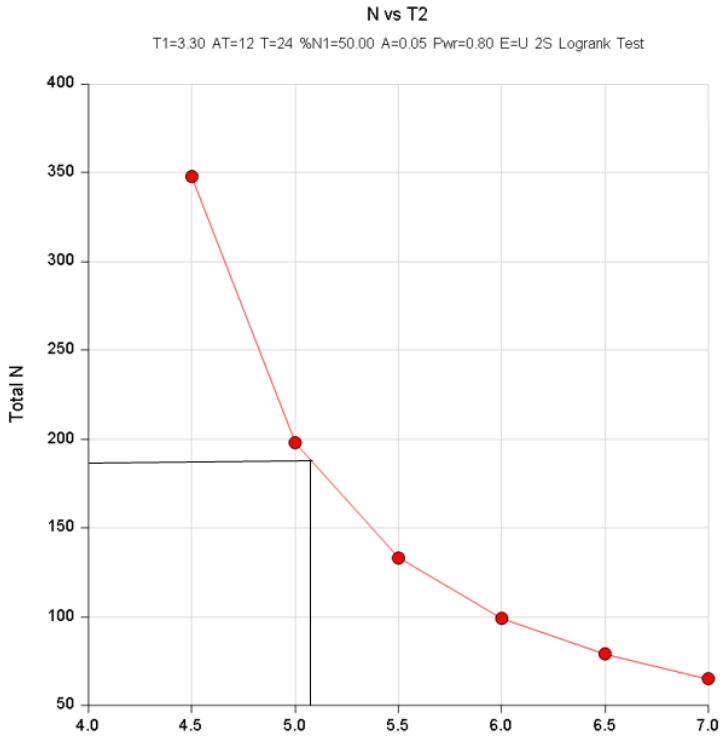


Figure 9-2: Progression-Free Survival Sample Size Plot: Total sample size requirement vs. the median survival time (month) in the treatment arm A



9.4 Randomization and Stratification

This study will be conducted at approximately up to 100 sites. A total of 218 subjects are planned to be enrolled. All eligible subjects 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.

9.5 Blinding

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.

9.6 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 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. Details of the firewall will be outlined in the SOP.

The results of the IA will be reviewed by an independent Data Safety and Monitoring Board (DSMB) who would 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.

Goals:

The objectives of this interim analysis are:

- To evaluate the safety and efficacy 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 to maintain study power.

9.6.1 Metrics to be Calculated for the Interim Analysis

9.6.1.1 Data for 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.

9.6.1.2 Data for Efficacy Interim Analysis based on Overall Survival (OS) and Progression Free Survival (PFS)

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 as described in Section 9.8.3.1.
    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 9.6.2:
    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 (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 below for both OS and PFS.

<u>Conditional Power (CP) using Differences in Overall Survival and Progression Free Survival</u>

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, [$S_k/\sqrt{\hat{I}_k}$], where S_k is the logrank score statistic computed from the observed data]

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 used to determine whether the sample size needs to be increased or remains unchanged.

9.6.2 Rules and Methods for Decisions at the Time of the IA

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 35% (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 and only if the interim analysis CP is less than 90% and greater than 35% then the sample size will be re-estimated up to 436 subjects by suing the PASS sample size calculation in Section 3.2. The sample size calculations will be performed under the same assumptions as the initial sample size calculations 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 IA.

The DSMB will make recommendations to sponsor on the continuation/modification/ termination and relevant comments based on the interim results.

9.6.3 Rule and Method for Protection 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 35%, performing an unblinded IA and sample size re-estimation will not have an effect 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%.

9.7 General Statistical Considerations

All collected study data will be presented in subject data listings or summarized. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

All the efficacy analyses presented here will be conducted using both the ITT and PP populations. All safety analyses will be conducted using the Safety population.

9.7.1 Analysis Populations

9.7.1.1 Intent-to-Treat (ITT) 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 and secondary endpoints.

9.7.1.2 Per Protocol (PP) 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.

9.7.1.3 Safety Population

The Safety population is defined as any subject receiving the treatment after randomization. This population will be used for the analysis of safety parameters.

9.7.2 Covariates

In the efficacy analysis, the pre-specified stratification factors stated in Section 9.4 will be included in the model.

9.7.3 Subgroups

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)

9.7.4 Missing data

For efficacy evaluation appropriate methods will be used to handle any missing data. The details of techniques for handling of missing data will be included in the SAP for the study which will be finalized prior to database lock.

9.8 Analysis Methods

A detailed SAP accompanies the protocol and any amendments to the SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this trial.

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 9.8.3.1. 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 endpoints, if tested, will use a two-sided analysis at an α=0.05 significance level.

9.8.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations will be summarized by treatment group, for all centers combined and each center separately. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

9.8.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group using appropriate descriptive statistics. Continuous variables will be summarized using the mean, median, standard deviation, minimum and maximum values by study treatment. Categorical variables will be summarized using frequency counts and percentages by study treatment. No inferential testing will be performed.

9.8.3 Efficacy Analyses

9.8.3.1 Primary Analysis

The primary analysis will be conducted on the Intent-to-treat (ITT) population. PP population will be used for supportive analysis to show the robustness of the analysis.

Primary Endpoints:

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. The order of the endpoints will be as follows:

1. Overall survival (OS)
   Overall survival time is defined as time from randomization to death from any cause or last day known to be alive.
2. 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.

OS and PFS will be compared between the treatment groups using stratified log-rank test with the stratification factors included in the model. The differences for treatment effect and its 95% CI will be estimated.

In addition, the Kaplan-Meier method will also be used to depict the median time to death from any cause for the treatment groups.

Secondary Endpoints:

Similarly, to maintain the trial-wise Type I error rate at 0.05, a hierarchical test procedure with fixed sequence 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 Carcinoma Antigen 19-9 (CA 19-9) response rate

Analysis of the secondary endpoints will be summarized according to the variable type:

- Continuous data summaries will include:
  - If the Normality assumption is met, Analysis of Covariance (ANCOVA) or Mixed Model using the stratification factor in the model.
  - If the Normality assumption is not met, a non-parametric method or a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data will be used.
- Categorical data summaries will be based on Logit model using the stratification factor in the model.

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

Similar analysis methods used for secondary endpoints will be applied to the analysis of the exploratory endpoints. Detailed analysis methods will be described in the SAP.

9.8.3.2 Supportive Analysis

To assess the consistency of the Primary Analysis results, supportive analysis will be conducted using the Per Protocol (PP) population. Statistical methodology for the supportive analyses will be the same as that of the primary analysis, with the exception of the analysis population used. The PP population will be used for the supportive analysis while ITT population will be used for the primary analysis.

9.8.3.3 Safety Analyses

The Safety population will be used for the analysis of safety endpoints.

For continuous variables data will be summarized by treatment using n, mean, SD, minimum and maximum values. For categorical variables data will be summarized by treatment using frequency and percentage. No inferential statistics are planned.

Adverse Events:

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Overall (i.e., regardless of severity or relationship to treatment)
- By severity grade (mild, moderate, severe, or life threatening for SAEs)
- By relationship to clinical trial treatment according to the mapping scheme below:
    - Potentially related: will include all adverse events with a relationship rating of "definitely", "probably" or "possibly".
    - Unlikely/not related: will include all adverse events with a relationship rating of "unlikely" or "unrelated".

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

Clinical Laboratory Data

All laboratory values will be listed. Laboratory measurements will also be summarized as continuous variable and presented by treatment group and time point.

Physical Examination

All physical examination findings will be listed and/or summarized.

Vital Signs

All vital sign findings will be listed and summarized.

10 Direct Access to Source Data/Documentation

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The monitors, auditors, personnel authorized by the Sponsor, the local IRB, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research and will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

11 Quality Control and Quality Assurance

11.1 Monitoring Requirements

In an effort to fulfil the obligations outlined in 21 Code of Federal Regulations (CFR) Part 312 and ICH guidelines which requires the Sponsor to maintain current personal knowledge of the progress of a study, the Sponsor's designated monitor will visit the center(s) during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

The Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all eCRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the eCRF. In addition to the original medical records, these data may include but are not limited to, study, laboratory and diagnostic reports, quality of life questionnaire, etc.

Site inspections serve to verify strict adherence to the protocol and the accuracy of the data being entered on the case report forms, in accordance with federal regulations. A Monitoring Log will be maintained at each study site which the monitor will sign, date and state the type of visit.

The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

For the IA, a cut-off date for data collection and monitoring will be determined and sites will be requested to provide current information up to the cut-off date.

11.2 Acceptability of electronic Case Report Forms (eCRFs)

eCRFs must be completed for each subject who has signed an informed consent form. For subjects who are screen failures, this would be limited to the screen failure eCRF page. All source documents and eCRFs will be completed as soon as possible after the subject's visit. Corrections to data on the eCRFs will be documented. The Investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. eCRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

11.3 Modification of Protocol

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator’s IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be in writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

11.4 Reporting Protocol Deviations

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the eCRFs.

11.4.1 Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. Examples of this include:

- 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.

11.4.2 Minor Protocol Deviation or Violation

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples of this include:

- Follow up visits that occurred outside the protocol required time frame because of the participant's schedule.
- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

12 Data and Safety Monitoring Board (DSMB)

The study will be monitored by an independent DSMB to ensure patient safety and to assess efficacy. The CRO is responsible for the overall management of DSMB, including development of its charter and membership selection. The DSMB will be managed in conformance with the FDA guidelines for DSMB independence, management, and oversight.

The DSMB will monitor the safety of the trial from the beginning and at approximately six month intervals based on enrolment thereafter.

The DSMB will consist of three members and will review all unexpected AEs, all related AEs, all SAEs, and all deaths during the Treatment and Follow-Up Phases. All expedited safety reports will be provided in real time to the DSMB chair upon being reported to FDA. At each meeting, the DSMB will be authorized to unblind the study upon unanimous vote in the event of any concerns about safety or lack of efficacy. Unblinded CRO personnel, separate and independent of the blinded CRO personnel, will supply the DSMB with all necessary tables and listings to perform their independent review. The Sponsor will be invited to attend open sessions where data remain blinded, but will not attend closed sessions where data are discussed in more detail with potential unblinding. The DSMB will make the following recommendations at each safety evaluation:

- Continue the study as planned;
- Assess a specific aspect of safety that is not conclusive;
- Gather more data to address a specific safety issue; and
- Stop the study due to safety concerns.

The DSMB will make the following additional recommendation at the efficacy evaluation:

- Continue the study as planned;
- Assess a specific aspect of efficacy that is not conclusive;
- Gather more data to address a specific efficacy issue; and
- Stop the study due to lack of efficacy.

The Sponsor retains the responsibility to contact FDA and the final decision regarding the recommendation to continue or to terminate the study.

A further description of the DSMB reporting requirements, meeting frequency, and the study stopping/continuation criteria can be found in the DSMB charter.

13 Ethics and Regulatory Requirements

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR Part 312, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, all study products used in this study are manufactured, handled and stored in accordance with applicable GMP and the products provided for this study will be used only in accordance with this protocol.

13.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The Principal Investigator (PI) at the site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

13.2 Investigator's Responsibilities

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any study centers participating in this study that cannot comply with these standards will be documented.

13.3 Subject Informed Consent Requirements

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the Investigator and/or designee. Written informed consent will be obtained from each subject before any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form ICF is to be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. Each study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject’s medical record, if allowed by institutional policy.

14 Data Handling and Record Keeping

14.1 Recording and Collection of Data

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve electronic case report forms (eCRF). The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and eCRFs will be completed as soon as possible after the subject's visit.

The Investigator will review eCRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and eCRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with the Lead Investigator.

The Investigator will maintain a confidential list of study subjects that will include each subject’s study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject’s case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

14.2 Clinical Data Management

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor’s or CRO’s standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor’s or the CRO’s SOPs as well as provisions of the study-specific Data Management Plan.

14.3 Archiving

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed eCRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- Product (e.g., IP, Standard Care supplies) and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening and randomization log
- SAE reports
- IRB approval and re-approval letters
- Completed quality of life questionnaires
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are subject to inspection by applicable health and regulatory agencies at any time.

15 Publication Plan

All information supplied by SynCore Biotechnology in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of SynCore Biotechnology, shall not be disclosed to others without the written consent of SynCore Biotechnology, and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of EndoTAG-1. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

Publication and Disclosure: Because this is a multi-center trial, the site and Investigator shall not independently publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities conducted under this protocol until such multi-center publication is released with the written approval and under the direction of Sponsor. Notwithstanding the foregoing, if a multi-center publication is not released within eighteen (18) months after completion of analysis of all study data from all studies conducted within the multi-center trial, both the site and Investigator shall have the right to publish the results of and information pertaining to the site's and Investigator's activities conducted under this protocol and the clinical trial agreement, subject to the prior review and written approval of Sponsor. The site and Investigator agree to submit any proposed manuscript, presentation or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the trial, even if the multi-center trial or the study is

terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

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17 Appendices

17.1 Appendix-I: EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

17.2 Appendix-II: EORTC QLQ - PAN26

EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did you feel weak in your arms and legs?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel the urge to move your bowels quickly?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Were you worried about your health in the future?	1	2	3	4
52. Were you limited in planning activities in advance (e.g. meeting friends)?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4