TITLE PAGE

PROTOCOL TITLE:	A Phase 3, Randomized, Double-Blind Study of Pamrevlumab or Placebo in combination with either Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX as Neoadjuvant Treatment in Patients with Locally Advanced, Unresectable Pancreatic Cancer
PROTOCOL NUMBER:	FGCL-3019-087
PHASE:	Phase 3
STUDY SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
KEY SPONSOR CONTACT(S):	Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile: [redacted] E-mail Address: [redacted]
IND NUMBER:	011952
EudraCT NUMBER:	2019-001925-28
STUDY DRUG:	Pamrevlumab (FG-3019)
INDICATION:	Locally Advanced Unresectable Pancreatic Cancer
ORIGINAL PROTOCOL:	05 November 2018
Amendment 1.0:	22 March 2019
Amendment 2.0:	27 September 2019
Amendment 3.0:	05 August 2020
Amendment 4.0:	25 October 2021
Amendment 5.0:	16 May 2022

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-Blind Study of Pamrevlumab or Placebo in combination with either Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX as Neoadjuvant Treatment in Patients with Locally Advanced, Unresectable Pancreatic Cancer

FGCL-3019-087

Original: 05 November 2018

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Amendment 5.0: 16 May 2022

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 FibroGen, Inc. 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, and any applicable local health authority, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen (or designee). Please retain the original for your study files.

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 05 November 2018

Amendment 1.0: 22 March 2019

Amendment 2.0: 27 September 2019

Amendment 3.0: 05 August 2020

Amendment 4.0: 25 October 2021

Amendment 5.0: 16 May 2022

This protocol (FGCL-3019-087) is approved by FibroGen.

IND Number: 011952

EudraCT Number: 2019-001925-28

*See appended final page for 21 CFR part 11compliant approval

[redacted] _____ _____

Date

FibroGen, Inc.

AMENDMENT 5.0: KEY CHANGES FROM AMENDMENT 4.0

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, flow, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Description of Key Change	Rationale for Change	Section(s) Affected
Per Protocol (PP) Population is added. Primary and secondary endpoints will also be conducted for PP population.	This will distinguish between ITT and PP Population.	Section 9.2.2
Objective Response Rate (ORR) was added as a secondary endpoint and the ordering of secondary endpoints was clarified.	ORR was added as a standard endpoint for oncology trials.	Protocol Synopsis, Sections 3.2.3, 9.3.4
Updates to exploratory endpoints	Quality of Life (QOL) endpoint has been changed to exploratory and will be analyzed by mixed effect model for repeated measurements (MMRM) model. Additionally, a new exploratory endpoint was included to compare the number of cycles completed between arms. Other administrative updates were made as well.	Protocol Synopsis, Sections 3.2.4, 9.3.4
Revised Exclusion Criteria 12, 13 and 14 and prohibited conmed sections	Removed specificity of exclusion criteria indicating that they only apply to subjects receiving G/NP chemotherapy as it may apply to other chemotherapy agents. Specified that caution should be used when administering CYP inhibitors or inducers to subjects receiving FOLFIRINOX. Specified that live vaccines should not be administered to subjects receiving FOLFIRINOX for 3 months post end of treatment.	Protocol Synopsis, Sections 5.2, 6.1.6.2.
Updated statistical methods	Statistical methods were revised/updated to align with updates made to Interim Analysis Plan and the Statistical Analysis Plan. Specifically, the objective of interim analysis of OS was changed to test lack of benefit from test of no harm.	Protocol Synopsis, Sections 9.1, 9.2.2., 9.3.1, 9.3.4.3, 9.3.4.4, 9.3.4.5, 9.3.4.6, 9.3.7 and 9.4

1. PROTOCOL SYNOPSIS

Study Title:	A Phase 3, Randomized, Double-Blind Study of Pamrevlumab or Placebo in combination with either Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX as Neoadjuvant Treatment in Patients with Locally Advanced, Unresectable Pancreatic Cancer
Protocol Number:	FGCL-3019-087
Investigational Product:	FG-3019 (Pamrevlumab)
Study Phase:	Phase 3
Indication:	Locally Advanced Unresectable Pancreatic Cancer
Number of Subjects Planned:	Approximately 280
Number of Sites Planned:	Approximately 100 (Global)

OBJECTIVES

Primary Objective:

- To evaluate the efficacy and safety of neoadjuvant treatment with pamrevlumab in combination with either gemcitabine plus nab-paclitaxel (G/NP) or FOLFIRINOX when compared to treatment with either G/NP or FOLFIRINOX alone in locally advanced, unresectable pancreatic cancer.

Secondary Objectives:

- To evaluate the effect of neoadjuvant treatment with pamrevlumab in combination with either G/NP or FOLFIRINOX on Event-Free Survival.

ENDPOINTS

Primary Endpoint:

- The primary endpoint is overall survival (OS), defined as the time from randomization to death due to any cause

Key Secondary Endpoint - Event-Free Survival (EFS) for Accelerated Approval:

- The EFS endpoint would be a composite time-to-event endpoint, the event being 'treatment failure' defined as the earliest occurrence of:
  a) Failure to achieve disease-free status locally after completion of neoadjuvant treatment and/or after surgery (i.e., resection failure or progression that precludes surgery)
  b) Local or distant recurrence, or
  c) Death

Secondary Endpoints:

- Progression-free survival (PFS), defined as the time from randomization until objective tumor progression or death (whichever occurs first)
- RECIST 1.1 – Best Overall Objective Response Rate (ORR), defined as the proportion of patients who achieve CR (Complete Response) or PR (Partial Response) during treatment period

Exploratory Endpoints:

- Change in Patient Reported Outcomes (PROs) as measured by:
  - Mean change from baseline during the treatment period in physical function by EORTC-QLQ-C30
  - Mean change from baseline during the treatment period in abdominal pain by NCI-PRO-CTCAE
  - Mean change from baseline during the treatment period in fatigue by NCI-PRO-CTCAE
- Proportion of all randomized subjects in whom R0 or R1 resection is achieved
- Difference in OS between resected and non-resected subjects
- The proportion of subjects considered eligible for surgical exploration per protocol-defined criteria
- Mean change from baseline during the treatment period in CA19-9
- Change in FDG-PET SUVmax and metabolic tumor volume (MTV) at EOT when compared to baseline
- Correlative analyses of baseline CTGF serum levels with clinical outcomes
- PK exposure-response analysis
- Histological analysis in tumor tissues collected during resection
- Evaluation of CTGF as prognostic/predictive biomarker
- Evaluation of other selected protein and nucleic acid markers in plasma samples
- Evaluation of number of chemotherapy cycles between the two arms

STUDY DESIGN

This is a Phase 3, randomized, double-blind trial to evaluate the efficacy and safety of neoadjuvant treatment with pamrevlumab or placebo in combination with either G/NP or FOLFIRINOX in the treatment of locally advanced, unresectable pancreatic cancer subjects. Approximately 280 subjects will be enrolled.

STUDY PERIODS

Screening Period (up to 30 days):

Subjects will be evaluated per the protocol inclusion/exclusion criteria to determine eligibility for participation in this trial. During screening, a central review board (including radiologists and surgeons) will confirm if subjects have locally advanced, unresectable disease prior to enrollment. This central review board will also review each subjects' baseline CT scan to determine the degree of superior mesenteric artery (SMA) encasement and whether or not they have unreconstructible disease for the purposes of stratification at randomization. The central review board will also evaluate subjects' baseline PET scan to determine SUVmax. Protocol assessments will be completed during screening visits in accordance with Schedule of Assessments (SOA) to establish a baseline profile, including: demographics, medical history, clinical status and disease stage for each subject. Subjects determined to be eligible for participation will be enrolled in the trial and randomized to study treatment. Investigators will choose the chemotherapy treatment regimen (either G/NP or FOLFIRINOX), in collaboration with their subjects, during the screening period.

Randomization:

Subjects will be randomized in a 1:1 ratio to one of the two study treatment arms; pamrevlumab with G/NP or FOLFIRINOX or placebo with G/NP or FOLFIRINOX. Subjects will be stratified at randomization by chemotherapy treatment regimen (G/NP or FOLFIRINOX), SMA encasement (> or ≤ 180 degrees), unreconstructible disease and geographic region.

Neoadjuvant Treatment Period (~24-30 weeks):

Subjects will receive up to 6 cycles of study treatment. Subjects' clinical status and safety will be regularly evaluated. Efficacy assessments will be performed routinely to evaluate subjects' quality of life and disease state. CT scans will be performed approximately every 8 weeks and evaluated by central imaging until disease progression is noted. If disease progression occurs during the neoadjuvant treatment period, subjects will be discontinued from study treatment and continue in the follow-up period. RECIST response will be evaluated by central radiology.

Eligibility Assessment for Surgical Exploration:

Eligibility for surgical exploration will be evaluated for all subjects who complete study treatment. To be considered eligible for surgical exploration a subject must meet at least one of the four protocol-defined criteria and have no contraindication to surgery, as outlined below:

The protocol-defined criteria for surgical eligibility are:

- Reduction in CA19-9 level ≥ 50%
- FDG-PET SUV_{max} decrease by ≥ 30% at EOT when compared to baseline
- Partial response [PR], complete response [CR], or stable disease [SD] per RECIST 1.1 at EOT
- Meet the definition of resectable or borderline resectable per NCCN® Version 2.2018

Contraindications to surgical eligibility are:

- Development of distant metastases or local progression per RECIST 1.1
- Performance status of Karnofsky score ≤ 50
- Unreconstructible disease as determined by central radiological/surgical review
- Other conditions that are considered by PI or surgeon to be contraindications to surgery

The site will be required to provide information to the central review board following the subject's EOT visit (i.e. CT scan, PET scan, CA19-9 values). The central review board will determine RECIST response, PET SUVmax response, unreconstructible disease and NCCN status. CA19-9 response will be determined by the central lab. The site will provide additional information to the central review board following the subject's Safety Follow-up Visit (i.e. subject performance status and a summary of any existing medical conditions/contraindications). Considering all the information provided, the central review board (to include radiologists, surgeons and oncologists) will then determine whether or not a subject is eligible for surgical exploration per protocol. The central review board will provide their assessment of surgical eligibility to the site within 5 business days of receipt of all required information (approximately 1 week after the Safety Follow-up Visit). After the recommendation from central review board is received at the site, the PI and surgeon will make the final decision as to whether or not a subject will undergo surgery. All instances of discordance between the determination of eligibility for surgical exploration by the central review board and the action taken by the site with regards to surgical exploration will be documented in the clinical database.

Subjects who undergo surgical exploration within the protocol specified window will be followed for surgical complications and outcomes per protocol. Tissue samples will be collected during resection and provided to central pathology.

Subjects who do not undergo surgical exploration (e.g. subjects who did not complete treatment or do not meet any of the protocol defined criteria or had a contraindication to surgery) will continue in the Follow-up period and receive treatment as per standard of care (SOC) for each institution.

Surgery:

Surgery will occur at least 4 weeks after the last dose (allowing for a wash-out period from treatment) and only after receipt of the recommendation from the central review board with regards to surgical eligibility. Surgery will occur no longer than 8 weeks after the last dose.

An outcome of R0 or R1 will be considered a 'Resection Achieved' while an outcome of R2 or partial resection will be considered a 'Resection Not Achieved'. Final surgical outcomes for all 'Resection Achieved' subjects will be determined by the central pathology lab. The sponsor/sites remain blinded to the central pathology lab assessments until their final analysis.

If a subject undergoes surgical exploration, but the surgeon is unable to perform resection (e.g. due to identification of metastases or extensive vascular involvement), it will be considered a 'Resection Not Attempted'.

Surgery will be performed in accordance with institutional standards and SOPs. Surgeons performing surgery for this study will be trained on the protocol, including criteria for surgical exploration. All subjects who undergo surgical exploration will be followed for surgical safety for 90 days (+/- 3 days) post discharge.

Safety Follow-up:

All subjects randomized will have a safety follow-up visit approximately 28 days after the last dose of study treatment and a final safety follow-up phone call at 60 days post last dose. However, if the investigator becomes aware of any serious adverse event that may be possibly related to study treatment after this protocol-required reporting period, the investigator may report the event to FibroGen within 24 hours following the investigator's knowledge of the event.

Follow-up Period:

Subjects will be followed for disease progression (if not previously detected) or recurrence following resection (local or distant recurrence). For subjects who complete treatment without evidence of disease progression and do not undergo resection, CT scans will continue to be performed approximately every 8 weeks and evaluated by central imaging until progression is detected (per RECIST 1.1). For subjects who undergo resection, follow-up CT scans to evaluate recurrence of disease will be evaluated by central imaging and performed approximately; every 4 months up to 2 years post-resection and every 6 months from 2 years to 5 years post-resection. The investigator may perform an "off schedule" CT scan at any time post resection if recurrence of disease is suspected clinically; these scans will be submitted to central imaging for review and confirmation of recurrence/disease progression. Subjects in follow-up will also be followed for any additional anti-cancer therapy received for their pancreatic cancer. All subjects will be followed for survival (until death) or until study closure (expected when the last subject to complete treatment reaches 18 months post-treatment).

Guidance was provided to all sites regarding conduct of this clinical trial during the COVID-19 global pandemic. Details are also captured within the body of the protocol.

SUBJECT ELIGIBILITY CRITERIA
Key Inclusion Criteria: • Understand and sign informed consent; be willing to comply with study procedures, including surgery • Age ≥18 years • Histologically or cytologically proven diagnosis of pancreatic ductal adenocarcinoma (PDAC) • Locally advanced and unresectable pancreatic cancer according to NCCN Guidelines® Version 2.2018 as determined by central imaging • Measurable disease as defined by Response Evaluation Criteria in Solid Tumors RECIST 1.1 criteria as determined by central imaging • ECOG performance status of 0 or 1 • Adequate liver, bone marrow, and renal function • Less than grade 2 pre-existing peripheral neuropathy
Key Exclusion Criteria: • Prior chemotherapy or radiation for pancreatic cancer • Previous (within the past 3 years) or concurrent malignancy diagnosis except non-melanoma skin cancer and in situ carcinomas (excluding in-situ breast cancer) • No major surgery for 4 weeks prior to signing consent form. Biliary stents are permitted. • Subjects with a history of; interstitial pneumonia, HCV, HBV or HIV infection • Subjects who have been administered a live vaccine within 4 weeks prior to the first administration of therapy • Subjects who cannot stop chronic medications that inhibit or induce CYP2C8 or CYP3A4

STUDY TREATMENT

Investigators and their subjects will choose to be treated with either Gemcitabine plus Nab-paclitaxel or FOLFIRINOX in combination with pamrevlumab or placebo in the neoadjuvant treatment period. Only one chemotherapy treatment regimen may be administered in combination with pamrevlumab or placebo during the treatment period.

Dose and Mode of Administration:

Study treatment will be administered in accordance with the schedule outlined below.

Pamrevlumab (or Placebo) - 35 mg/kg, IV, Days 1 and 15 of each cycle; additional dose given on Day 8 of Cycle 1 only

and

Gemcitabine - 1000 mg/m^2 by IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle

Nab-paclitaxel - 125 mg/m^2 by IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle

OR

FOLFIRINOX

Oxaliplatin – 85 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle

Folinic Acid/Leucovorin – 400 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle

Irinotecan* – 180 mg/m^2 by IV infusion on Days 1 and 15 of each 28-day treatment cycle

Fluorouracil* – 400 mg/m^2 by IV infusion (bolus infusion) on Days 1 and 15 of each 28-day treatment cycle

Fluorouracil – 2400 mg/m^2 by IV infusion (46 hour continuous infusion) on Days 1-3 and Days 15-17 of each 28 day treatment cycle

*Doses may be adjusted per local/institutional guidelines to support modified FOLFIRINOX dosing regimen (mFOLFIRINOX)

Other Important Information:

Regular supportive care as clinically indicated is permitted during this trial.

Pamrevlumab should not be administered to subjects with a history of allergic or anaphylactic reaction to human, humanized, or chimeric monoclonal antibodies.

Gemcitabine, nab-paclitaxel or FOLFIRINOX should not be administered to subjects with a history of allergic or anaphylactic reaction to these products or their excipients.

Interactions between the gemcitabine, nab-paclitaxel or FOLFIRINOX and concomitant medications are described in their respective package inserts/SmPCs.

In accordance with the product package insert (SmPC), certain drugs that inhibit or induce CYP3A4 or CYP2C8 should be used with caution in subjects receiving the Nab-paclitaxel or FOLFIRINOX.

Live vaccines are prohibited for subjects receiving the G/NP or FOLFIRINOX chemotherapy regimen during the treatment period and for 3 months after the last dose of study therapy.

Female subjects of childbearing potential are required to use highly effective contraception methods during the conduct of the study and for 6 months after the last dose of study drug.

Male subjects with partners of childbearing potential are required to use highly effective contraception methods during the conduct of the study and for 6 months after the last dose of study drug.

DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established. A DMC charter will establish the rules, meeting frequency, and scope of responsibilities of the committee.

STATISTICAL METHODS

Sample Size Calculations:

The study is planned to enroll approximately 280 subjects with 1:1 randomization ratio to the two treatment arms. This sample size is estimated based on the assumption that the median OS for the pamrevlumab arm and the placebo arm are 24 and 16.3 months, respectively. This improvement represents a hazard ratio (HR) of 0.68. With this HR, 233 deaths will provide at least 80% power with a significance level of 0.05. With the enrollment of approximately 280 subjects, 233 deaths are estimated by the end of the Follow-up period.

Based on the treatment effect on EFS has a hazard ratio 0.60, then 161 events would be required to provide 75% power when using a stratified log-rank statistic with (one-sided) 0.005 false positive error rate.

Statistical Analysis Methods:

Event free survival (EFS) will be used as a surrogate endpoint for OS at a pre-planned interim analysis. A hierarchical approach for analysis is described. If the interim analysis of the effect of pamrevlumab on EFS is statistically significant at two-sided p=0.01, then that alpha will be carried forward to the final analysis of OS, which then would be conducted at the two-sided p=0.05 level. If the effect of pamrevlumab on EFS is not statistically significant at two-sided p=0.01, then the final analysis of pamrevlumab's effect on OS would be conducted at the two-sided p=0.04 level.

At the time approximately 161 EFS events occur in the trial (or more depending on completion of accrual), the DMC will conduct an interim look of OS for lack of benefit analysis, using an O'Brien-Fleming monitoring boundary, if the EFS analysis rejects the null hypotheses at an alpha level of 0.01. Following the completion of the interim analysis for EFS/OS, procedures will be in place to avoid pre-judgment of OS data by properly maintaining its confidentiality until final OS analysis is complete or unless there is agreement with the Regulatory agency to do otherwise.

All efficacy endpoints will be analyzed using the ITT or PP population and safety will be analyzed using the safety population.

The OS, event-free survival (EFS), and progression-free survival (PFS) endpoints will be analyzed using the Cox proportional hazard model adjusting for randomization stratification factors.

The exploratory endpoints of mean change from baseline during the treatment period in physical function by EORTC-QLQ-C30, mean change from baseline during the treatment period in abdominal pain by NCI-PRO-CTCAE, mean change from baseline during the treatment period in fatigue by NCI-PRO-CTCAE will be analyzed using a MMRM model. All analyses will be adjusted by the randomization factors.

Resection rate will be analyzed using Cochran-Mantel-Haenszel (CMH) test adjusting for randomization stratification factors.

Continuous variables will be presented by descriptive statistics: n, mean, standard deviation or standard error, median, minimum, and maximum. Categorical variables will be presented by counts of subjects and percentage. Two-sided 95% confidence intervals will be included for the key efficacy parameters.

Safety Analyses:

Treatment-emergent adverse events (TEAEs) will be summarized by treatment arm. Treatment-emergent deaths, serious TEAEs, TEAEs with grade 3 or 4 per CTCAE criteria, and TEAEs leading to study or treatment discontinuation will be summarized separately.

Surgical complications, clinically significant changes from baseline in vital signs, laboratory tests, and ECGs will be assessed.

Human anti-human antibody data will be summarized in a separate report.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents.

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2. INTRODUCTION

2.1. Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G1 (IgG) kappa monoclonal antibody that binds to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2. Locally Advanced Unresectable Pancreatic Cancer

Pancreatic ductal adenocarcinoma is an aggressive cancer with poor prognosis; the median OS is 5 to 8 months and 5-year survival is 8.2% (SEER, 2018). This positions PDAC to have the worst outcome of all gastrointestinal cancers and the fourth leading cause of cancer related mortality. The incidence of PDAC increased by 1.2% annually between 2000 and 2012, likely due to increasing incidences of obesity and type II diabetes mellitus in the US and worldwide (American Cancer Society, 2016).

Pancreatic cancer has notably been resistant to chemotherapy. Gemcitabine alone has been shown to improve PFS and OS and was approved for use in locally advanced and metastatic pancreatic cancer in 1996 (Burris 1997). Most clinical studies in PDAC focus on patients with metastatic disease and have demonstrated only modest improvements in OS. Recently approved therapies include nab-paclitaxel in combination with gemcitabine, which improved OS by 1.8 months compared with gemcitabine alone, and FOLFIRINOX [oxaliplatin, irinotecan, 5-FU, and leucovorin]) alone, which improved OS by 3.7 months compared to gemcitabine (Von Hoff 2013; Conroy 2011).

In general, surgical resection offers patients the best chance at long-term survival (5 year survival 27%) and possibly a cure, but the majority of patients present with advanced unresectable disease at the time of diagnosis. A large meta-analysis of available therapies from 1996 to 2009 reported that neoadjuvant therapy increased the resectability rate in unresectable and borderline resectable patients to 30%, with the increase of median OS from 10.2 months to 20.5 months (Gillen 2010). This data provides a strong rationale for neoadjuvant therapy followed by resection in order to improve OS in LAPC. However, no SOC exists for neoadjuvant therapy in patients with LAPC.

Recent trials in LAPC have explored the effects of single agent chemotherapy in combination with radiotherapy on OS (Mukherjee 2013). A 6-months treatment with standard-of-care chemotherapy alone or chemo-radiation in patients with LAPC only led to a 6% surgical resection rate in treated patients, with a median follow-up of 36.7 months, the median overall survival from the date of the first randomization was not significantly different between chemotherapy at 16.5 months and chemoradiotherapy at 15.2 months ($p = 0.83$). Although the LAP07 trial failed to show a survival benefit with the use of radiation therapy (Hammel 2016), other trials (e.g., ECOG 4201 [Loehrer 2011]) have led to the opposite conclusion. In terms of

treatment, there has also been an increased interest in combination chemotherapies followed by surgery with curative intent (Dean 2016, Hammel 2016) for LAPC patients.

In the LAPACT trial, the neoadjuvant therapy with gemcitabine/nab-paclitaxel was used in 110 LAPC patients for 6 cycles. The resection rate established in this trial was 15%, and 1 year OS rate was 72% (long term OS not reported to date). This trial establishes benchmark resection rate for LAPC patients following combination therapy with gemcitabine/nab-paclitaxel (Hammel 2018).

Significant progress has been made in recent years with systematic chemotherapies of LAPC. In a study using a nab-paclitaxel plus gemcitabine combination, 77% of 177 patients had at least a 50% reduction in CA19-9 levels, and CA19-9 response was found to be an independent prognostic factor for OS (Reni 2017). In the LAPACT study, serum CA19-9 concentrations decreased after 6 cycles of chemotherapy in most patients and 15 % of them underwent curative-intent surgery (Philip 2020). In a meta-analysis about FOLFIRINOX in LAPC, the authors reported a median OS of 24.2 months; in addition, 25 (9%) of patients could have a surgical resection, of whom 78 (4%) had an R0 resection (Suker 2016).

In LAPC, a novel endpoint is needed that would have considerable reliability in predicting the effects on OS of both neoadjuvant therapies and surgical resection. Surgery has not only a therapeutic role in LAPC, but also a diagnostic role in our proposed definition of EFS, in that it is used to assess local disease-free status at the end of induction therapy. However, to achieve sensitivity as well to the presence and the impact of microscopic distal disease, the proposed definition of EFS is based on time to detected disease, either through surgery for local disease or, in a manner analogous to 'DFS in the adjuvant setting,' through subsequent detection of local or distal disease by CT, or to death.

The LAPC patient population represents a high unmet need as no standard of care has been established in prospective, randomized trials. At the same time, increasing efficacy of neoadjuvant therapies in LAPC justifies revisiting study endpoint in order to better reflect treatment efficacy beyond effects on duration of OS. Based on our nonclinical tumor model data and clinical data we believe that pamrevlumab with its antifibrotic mechanism of action and when combined in a neoadjuvant setting with SOC chemotherapy, may provide the unique opportunity to impact both event-free survival in LAPC and OS.

2.2.1. Relevance of Connective Tissue Growth Factor (CTGF) in Pancreatic Cancer

Connective tissue growth factor is a secreted glycoprotein produced by fibroblasts and myofibroblasts, endothelial cells, activated stellate cells, and other cell types. Its expression is induced by a variety of regulatory modulators, including TGF-β and vascular endothelial growth factor, as well as environmental conditions such as hypoxia, pressure, and increased tissue stiffness. Cellular functions modulated by CTGF include secretion and/or organization of extracellular matrix, cell proliferation, survival, adhesion, migration, and epithelial to mesenchymal transition. These biological activities are associated with aberrant tissue repair (i.e., fibrosis) and tumorigenesis. Elevated CTGF expression is detected in many tumor types, in particular, PDAC and invasive breast carcinoma (Wenger 1999, Xie 2001). Among 19 samples of pancreatic tumors, 15 showed an average 59-fold increase of CTGF expression, compared with a 4.5-fold increase observed in chronic pancreatitis (Wenger 1999). CTGF was identified as

an invasion-specific gene in PDAC (Ryu 2001) and is highly expressed within the neoplastic epithelium (Iacobuzio-Donahue 2002). In any specific tumor, CTGF can be expressed by PDAC tumor cells, by stellate or stromal cells within the tumor, or by both cell types (Hidalgo 2012, Wenger 1999, Iacobuzio-Donahue 2002, Frazier 1997, Hartel 2004).

2.3. Rationale

2.3.1. Nonclinical Studies

FibroGen has evaluated the efficacy/pharmacology, pharmacokinetics and nonclinical safety of pamrevlumab per ICH guidelines to support the clinical development of pamrevlumab in pancreatic cancer. Pharmacodynamic studies were conducted in various tumor models to evaluate pamrevlumab as a modulator of tumor cell survival, chemoresistance, and tumor cell invasion/migration. The pharmacokinetics of pamrevlumab have been characterized following single oral doses in rats, rabbits, and monkeys and after repeated oral doses in toxicity studies in mice, rats, rabbits and monkeys. The nonclinical safety of pamrevlumab was evaluated in repeated dose toxicity studies in mice, rats and monkeys. Cross-Reactivity studies with pamrevlumab have been conducted with mouse and human tissues. The potential effects of pamrevlumab on wound healing have been evaluated in an abdominal wound healing model in rats.

Summaries of all completed, nonclinical studies supporting the pancreatic cancer indication can be found in the current version of the Investigator's Brochure.

2.3.2. Clinical Studies

Pamrevlumab is in clinical development for the treatment of pancreatic cancer. The Sponsor has conducted 2 clinical studies in pancreatic cancer: Study FGCL-MC3019-028 (Study 028) was completed in June 2014 and Study FGCL-3019-069 (Study 069) in which the study treatment and surgery periods have been completed and analyzed.

The results of Study 028, an open label study, indicate that pamrevlumab can be safely combined with gemcitabine and erlotinib without increased toxicity in advanced Stage 3 and Stage 4 pancreatic cancer patients. The efficacy results (including positive drug-biomarker activity) show potential survival benefit with pamrevlumab treatment, combined with gemcitabine and erlotinib, particularly in subjects with higher Day 15 pamrevlumab Cmin values. These results underscore the potential validity of combined treatments that target both stroma and cancer cells in PDAC. Finally, the results also indicate the potential value of CTGF as a predictive biomarker and support further evaluation of pamrevlumab in combination with chemotherapy in a properly controlled and adequately powered study comparing SOC chemotherapy to SOC plus pamrevlumab.

The encouraging results from Study 028 led to the initiation of the Phase 1/2 study, Study 069, using gemcitabine/nab-paclitaxel +/- pamrevlumab in a neoadjuvant setting.

In Study 069, the addition of pamrevlumab to gemcitabine and nab-paclitaxel appears to positively impact eligibility for surgical exploration and resection rates in the treatment arm when compared to control. Seventy-one percent (17/24 patients) were eligible for surgical exploration in the treatment arm compared to 15% (2/13 patients) in the control arm. Thirty-three percent (8/37 patients) were resected in the treatment arm (4-R0, 4-R1) compared to 8% (1/13

patients) in the control arm (1-R0). The expanded criteria used to determine surgical eligibility by inclusion of CA 19.9 and PET response allowed patients who otherwise would not be eligible to undergo surgical exploration.

In this ongoing study, the TEAEs have been similar to what was seen in the previous pancreatic cancer study with pamrevlumab (Study 028) and are consistent with what has been observed in pancreatic cancer patients treated with gemcitabine and nab-paclitaxel. To date, there are no apparent safety signals associated with the addition of pamrevlumab to gemcitabine and nab-paclitaxel, and the triple combination appears to be well tolerated by subjects with LAPC.

The improved eligibility for surgical exploration and resection rates in the treatment arm when compared to the control, provide direct rationale for the development of a larger Phase 3 study.

Summaries of all completed, clinical studies supporting the pancreatic cancer indication can be found in the current version of the Investigator's Brochure.

2.3.3. Dose Rationale

Analysis of data from a dose finding study FGCL-3019-028 (Study 028) supported the dose regimen used in the Phase 1/2 study FGCL-3019-069 (Study 069). In Study 028, pamrevlumab was tested in combination with gemcitabine and erlotinib in subjects with Stage 3 or 4 pancreatic adenocarcinoma.

The efficacy analyses indicated potential survival benefit, particularly in those subjects with greater pamrevlumab Day 15 C_{min} values. Higher pamrevlumab C_{min} values lower baseline CTGF levels (<median) were associated with longer median OS and higher 1-year OS rates, prolonged PFS, and CA19-9 reductions in this study population. For example, a Day 15 C_{min} level ≥ 150 µg/mL compared to < 150 µg/mL was associated with statistically significantly longer OS (9.0 vs 4.4 months [p=0.0244]) and a greater proportion of subjects surviving to at least 1 year (34.2% vs 10.8% [p=0.0258]).

The analysis of final data showed that a pamrevlumab dose of 35 mg/kg given biweekly resulted a mean Day 15 C_{min} values of > 150 µg/mL (mean ± SD of 169 ± 47 µg/mL). The next dose level (45 mg/kg biweekly) did not increase the mean Day 15 C_{min} values (mean ± SD of 166 ± 63 µg/mL). Therefore, a dose of 35 mg/kg biweekly is supported based on these efficacy analyses.

Additionally, a dose justification evaluation was performed with data from Phase 1 dose escalation studies as well as data from FGCL-3019-028 and FGCL-3019-069 using exposure-efficacy analysis. The summary of the exposure-efficacy analysis is below:

Justification for Pamrevlumab Dose of 35 mg/kg Q2W for LAPC

- A regimen of pamrevlumab of 35 mg/kg Q2W increases the percent of subjects eligible for surgery and achieving resection in LAPC.
- Exposure-response models for resection predicts that increasing the dose to 45 mg/kg Q2W only increases the probability of resection by 2% while decreasing the dose to 25 mg/kg Q2W decreases the probability by 4%

Secondary Evidence from Study 028 (88% Metastatic)

- The dose-response (1-yr OS) model predicts that OS plateaus beyond 25 mg/kg. The dose-response model predicts that increasing the dose from 35 to 45 mg/kg Q2W only increases the probability of 1-yr OS by 1%, while decreasing the dose to 25 mg/kg Q2W decreases the probability by 4%.

Safety Assessment

- No relationship between reported serious TEAEs and exposure when pamrevlumab was combined with Gemcitabine and Erlotinib (Study 028)
- No relationship between reported serious TEAEs when pamrevlumab was combined with Gemcitabine and Nab-paclitaxel (Study 069)

Based on the above, the dose regimen and duration for this study is the same as previously evaluated in Study FGCL-3019-069 (35 mg/kg Q2W). This dose will be administered in combination with either the G/NP or FOLFIRINOX treatment regimen.

2.3.4. Safety Summary

In Study 028, pamrevlumab was tested in combination with gemcitabine and erlotinib in chemotherapy naïve subjects with Stage 3 and 4 pancreatic adenocarcinoma. All 75 subjects were included in the Safety population and at least 1 TEAE was reported for each. A total of 65 subjects had ≥ 1 TEAE following the first dose of pamrevlumab but prior to the administration of other study drugs. The most frequently reported TEAEs after the administration of pamrevlumab and prior to gemcitabine and erlotinib were nausea, abdominal pain, constipation, decreased appetite, and fatigue. The most common TEAEs reported following the administration of chemotherapy were: fatigue, nausea, diarrhea, vomiting, and abdominal pain. There was no apparent imbalance between the cohorts or dose dependent effect in the type or severity of TEAEs.

In Study 069, 37 subjects were enrolled in an overall 2:1 ratio to one of two treatment arms; pamrevlumab with gemcitabine plus nab-paclitaxel (Arm A) or gemcitabine plus nab-paclitaxel alone (Arm B). Twenty-four subjects were randomized to Arm A and 13 subjects were randomized to Arm B. All 37 subjects were included in the Safety population. Overall, a total of 36 subjects had at least 1 TEAE; 24 subjects in Arm A and 12 subjects in Arm B. The most common TEAEs reported in Arm A vs. Arm B were: fatigue (75.0% vs 76.9%), nausea (70.8% vs 53.8%), alopecia (66.7% vs 53.8%), edema peripheral (58.3% vs 38.5%), decreased appetite (50% vs 38.5%) and diarrhea (50.0% vs 53.8%).

The only TEAE assessed by the Investigator as possible related to pamrevlumab but not to gemcitabine/nab-paclitaxel was an influenza like illness in one subject that was Grade 1 and non-serious. The majority of TEAEs reported are listed as an adverse drug reaction in the product labeling for gemcitabine and/or nab-paclitaxel.

There were no notable changes in laboratory results, vital signs, electrocardiograms, or physical findings. Overall, TEAEs were typical of those observed in subjects with the underlying medical condition and/or typical of adverse reactions associated with gemcitabine and nab-paclitaxel. To date, there are no apparent safety signals associated with the addition of pamrevlumab to

gemcitabine and nab-paclitaxel, and the triple combination appears to be well tolerated by subjects with LAPC.

No deaths secondary to AEs and/or related to pamrevlumab were reported.

For additional information on the safety of pamrevlumab in pancreatic cancer patients and in other indications, please refer to the current version of the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objective

The primary objective of this trial is to evaluate the efficacy and safety of neoadjuvant treatment with pamrevlumab in combination with either gemcitabine plus nab-paclitaxel (G/NP) or FOLFIRINOX when compared to treatment with G/NP alone or with FOLFIRINOX alone in locally advanced, unresectable pancreatic cancer.

3.1.2. Secondary Objectives

The secondary objective of this trial is to evaluate the effect of neoadjuvant treatment with pamrevlumab in combination with either G/NP or FOLFIRINOX on event-free survival.

3.2. Endpoints

3.2.1. Primary Endpoint

The primary endpoint of this trial is overall survival (OS), defined as the time from randomization to death due to any cause.

3.2.2. Key Secondary Endpoint - Event-Free Survival (EFS) for Accelerated Approval

The EFS endpoint is a composite time-to-event endpoint, the event being 'treatment failure' defined as the earliest occurrence of:

a. Failure to achieve disease-free status locally after completion of neoadjuvant treatment and/or after surgery (i.e., resection failure or progression that precludes surgery); or
b. Local or distant recurrence; or
c. Death

3.2.3. Secondary Endpoints

The secondary endpoints of this trial are:

- Progression-free survival (PFS), defined as the time from randomization until objective tumor progression or death (whichever occurs first) [Ref: https://www.fda.gov/media/71195/download]
- RECIST 1.1 – Best Overall Objective Response Rate (ORR), defined as the proportion of patients who achieve CR (Complete Response) or PR (Partial Response) during treatment period

All secondary endpoints of this trial will be tested hierarchically in the order listed above.

3.2.4. Exploratory Endpoints

Exploratory endpoints for this trial are:

- Change in Patient Reported Outcomes (PROs) as measured by:
  - Mean change from baseline during the treatment period in physical function by EORTC-QLQ-C30
  - Mean change from baseline during the treatment period in abdominal pain by NCI-PRO-CTCAE
  - Mean change from baseline during the treatment period fatigue by NCI-PRO-CTCAE
- Proportion of all randomized subjects in whom R0 or R1 resection is achieved.
- Difference in OS between resected and non-resected subjects
- The proportion of subjects considered eligible for surgical exploration per protocol defined criteria
- Mean change from baseline during the treatment period in CA19-9
- Change in FDG-PET SUVmax and metabolic tumor volume (MTV) at EOT when compared to baseline
- Correlative analyses of baseline CTGF serum levels with clinical outcomes
- PK exposure-response analysis
- Histological analysis in tumor tissues collected during resection
- Evaluation of CTGF as prognostic/predictive biomarker
- Evaluation of other selected protein and nucleic acid markers in plasma samples
- Evaluation of number of chemotherapy cycles between the two arms

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 3, randomized, double-blind trial to evaluate the efficacy and safety of neoadjuvant treatment with pamrevlumab or placebo in combination with either G/NP or FOLFIRINOX, in the treatment of locally advanced unresectable pancreatic cancer (LAPC) subjects. Approximately 280 subjects will be enrolled in this trial, across approximately 100 study centers in the following locations: North America, Europe and Asia Pacific.

Investigators will have the option to choose between prescribing either G/NP or FOLFIRINOX prior to randomization.

Subjects will be randomized in a 1:1 ratio to the addition of either pamrevlumab or placebo to the prescribed chemotherapy treatment regimen (G/NP or FOLFIRINOX). Subjects will be stratified at randomization by chemotherapy treatment regimen (G/NP or FOLFIRINOX), SMA encasement (> or ≤ 180 degree), unreconstructible disease and geographic region.

This trial has five study periods:

- Screening
- Neoadjuvant Treatment
- Evaluation for Surgical Exploration
- Surgery
- Follow-up

In the screening period, subjects will be evaluated per the protocol inclusion/exclusion criteria to determine eligibility for participation in this trial. Protocol assessments will be completed during the screening period in accordance with SOA (see Appendix 1) to establish a baseline profile, including: demographics, medical history, clinical status and disease stage for each subject. During screening, a central review board (including radiologists and surgeons) will confirm subjects have locally advanced, unresectable disease prior to enrollment. This central review board will also review each subjects' baseline CT scan to determine the degree of SMA encasement and whether or not they have unreconstructible disease for the purposes of stratification at randomization. See Section 7.1.1 for details.

In the Neoadjuvant Treatment period, randomized subjects will receive up to 6 cycles (~24-30 weeks) of study treatment. Subjects' clinical status and safety will be evaluated regularly along with efficacy assessments to evaluate subjects' quality of life and disease state as described in Section 7 and the SOA (Appendix 1). If disease progression is noted during the treatment period, subjects will be discontinued from study treatment. Subjects who discontinue treatment early for any reason will complete End of Treatment (EOT) visit and continue in the Follow-up period. Subjects who complete study treatment will be evaluated to determine eligibility for surgical exploration and may undergo surgical resection prior to continuing in the Follow-up period.

For overall Safety Follow-up, all subjects enrolled will have a safety follow-up visit approximately 28 days after the last dose of study treatment and a final safety follow-up phone

call at approximately 60 days post last dose. For details regarding safety follow- up and reporting, see Section 8.

Eligibility for surgical exploration will be evaluated for all subjects who complete study treatment (i.e. at least 11 of 13 planned doses of pamrevlumab or placebo and at least one dose of pamrevlumab or placebo in each cycle and no withdrawal of treatment due to AE or other reasons). The site will be required to provide information following the subject's EOT visit (i.e. CT scan, PET scan, CA19-9 values) and Safety Follow-up Visit (i.e. performance status and a summary of any existing medical conditions/contraindications) to the central review board (to include radiologists, surgeons and oncologists) who will then determine whether or not a subject is eligible for surgical exploration per protocol. The central review board will provide their assessment of surgical eligibility to the site within 5 business days of receipt of all the required information (approximately 1 week after the Safety Follow-up Visit). After the recommendation from central review board has been received by the site, the PI and surgeon will make the final decision as to whether or not a subject will undergo surgery. All instances of discordance between the determination of eligibility for surgical exploration by the central review board and the action taken by the site with regards to surgical exploration will be documented in the clinical database. See Section 7.1.3 for details.

Subjects who do not undergo surgical exploration (e.g. did not complete study treatment, do not meet any of the protocol-defined criteria for surgical eligibility or have a contraindication to surgery, or site decision not to proceed with surgery) will continue in the Follow-up period and be followed for progression, survival and additional anti-cancer therapies.

Surgery will occur at least 4 weeks after last dose (allowing for a wash-out period from treatment) and only after receipt of the recommendation from the central review board with regards to surgical eligibility. Surgery will occur no longer than 8 weeks after the last dose.

An outcome of R0 or R1 will be considered a 'Resection Achieved' while an outcome of R2 or partial resection will be considered a 'Resection Not Achieved'. Final surgical outcomes (R0 and R1) for all 'Resection Achieved' subjects will be determined by the central pathology lab. The sponsor/sites remain blinded to the central pathology lab assessment until their final analysis.

If a subject undergoes surgical exploration, but the surgeon is unable to perform resection (e.g. due to identification of metastases or extensive vascular involvement), it will be considered as 'Resection Not Attempted'.

All subjects who undergo surgical exploration within the protocol specified window will have tissue collected and sent to central pathology for review and will be followed for surgical complications for 90 days post discharge.

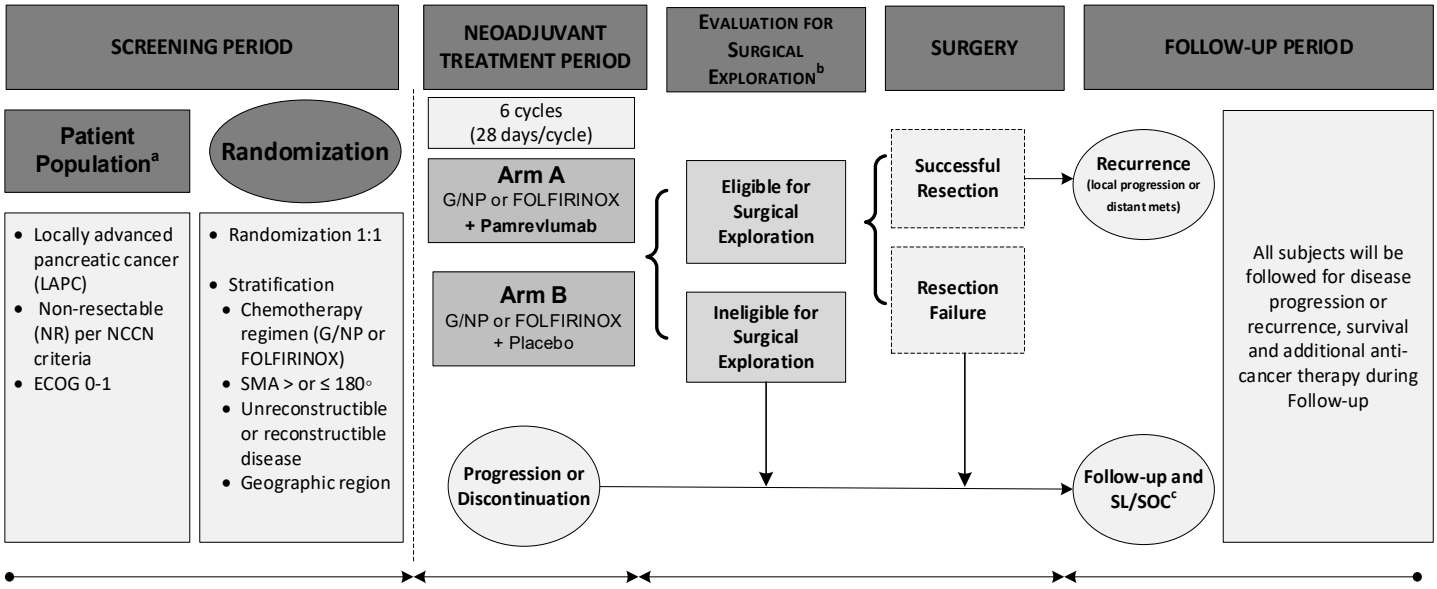
In the Follow-up period, all subjects will be followed for disease progression (if not previously detected) or recurrence (local or distant) following resection. Subjects will be followed for survival and any additional anti-cancer therapy received for their pancreatic cancer until the last subject to complete treatment has been followed for approximately 18 months post-last dose (i.e. at this time it is expected that 233 death events will have occurred to support final analysis of OS). Subjects may receive second line therapy at the investigator's discretion.

A schematic overview of the study is provided in Figure 1. A detailed overview of assessments and the timing of assessments is provided in Appendix 1 and 2.

4.1.1. Estimated Study Duration

It is anticipated that enrollment will be complete within 3-4 years from first subject enrolled. All subjects will complete up to 6 cycles of study treatment and at least 60 days of safety follow-up post last dose. All subjects will be followed in the Follow-up Period until the total number of deaths reported reaches 233 or the sponsor terminates the study. It is anticipated that 233 deaths will occur by the time the last subject to complete treatment has been followed for approximately 18 months. Therefore, some subjects could remain on study for approximately 6 years.

Figure 1: FGCL-3019-087 Study Schema



Abbreviations: G=Gemcitabine; NP=Nab-Paclitaxel; PD=Progressive Disease; SL=Second Line Therapy; SOC=Standard of Care
[a]Central review team (including radiologists and surgeons) will confirm subjects have locally advance unesectable disease prior to enrollment. See Section 7.1.1.1 for details.
[b]Subjects must meet at least ONE of the four protocol-defined criteria, which include; CA19-9 decline ≥ 50%, PET SUVmax decline > 30%, RECIST response (CR, PR or SD), resectable or borderline resectable per NCCN and have NO contraindication to surgery. A central review team (including radiologists, surgeons and oncologists) will determine whether a subject is eligible for surgical exploration per protocol. See Section 7.1.4 and 7.1.4.1 for details.
[c]Second-Line Treatment may be administered as per the investigator/institutional SOC

4.1.2. Randomization

Approximately 280 subjects will be prescribed treatment with either G/NP or FOLFIRINOX, and then randomized 1:1 to receive either pamrevlumab or placebo, resulting in approximately 140 subjects per treatment arm. Each subject will receive a unique study ID number in the screening and randomization process. Details are outlined in the randomization plan.

Subjects will be stratified at randomization according to the following factors:

- Chemotherapy treatment regimen (G/NP or FOLFIRINOX)
- SMA encasement (> or ≤ 180°)
- Unreconstructible disease (yes or no)
- Geographic region (North America/Europe or Asia Pacific)

Each region represents a specific surgical skills or general surgical outcomes and as subjects are randomized, the Interactive Response System (IXRS) will assign the treatment arms dynamically to ensure an equal distribution of subjects in both treatment groups across each region. Countries will be assigned to one of the two regions based on their general standard of care and surgical performance.

4.1.3. Treatment Assignment

Within each stratum, subjects will be randomized 1:1 to one of two treatment arms:

Arm A: pamrevlumab + either G/NP or FOLFIRINOX

Arm B: placebo + either G/NP or FOLFIRINOX

4.2. Blinding

This is a double-blind, placebo-controlled study. The Investigator, study site staff, subjects, and selected Sponsor study team and designees are blinded to study drug assignment.

4.2.1. Maintenance of Blinding

The study blind will be maintained for all parties specified above throughout the study with the exception of the scenarios outlined in Section 4.2.2. and 4.2.3. Pamrevlumab and placebo will be identical in appearance, packaging, and labeling in order to maintain the study blind.

4.2.2. Planned and Unplanned Unblinding of Treatment Assignment

Investigators, study site staff and subjects will remain blinded to treatment assignments until study completion.

Any unplanned, intentional or unintentional, breaking of the blind should be reported and documented. Breaking the blind (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the Investigator for the subject's care. All Principal Investigators are granted access to the IRT system and assigned a role which will allow them to rapidly unblind a patient in the event of an emergency. It is not required to discuss this action with the sponsor (or designee) prior to its execution.

4.2.3. Unblinding of Treatment Assignment for Interim Analysis

Details regarding the maintenance of the blind for the study team, sites and other staff during the interim analysis will be provided in a Data Access Plan.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

In order to be eligible for inclusion in this trial, a subject must meet all of the following:

1. Understand and sign informed consent; be willing to comply with study procedures, including surgery
2. Age ≥ 18 years
3. Be a male, or non-pregnant and non-lactating female
4. Negative serum B-hCG pregnancy test at screening for women of childbearing potential
5. Male subjects with partners of childbearing potential and female subjects of childbearing potential are required to use highly effective contraception methods during the conduct of the study and for 6 months after the last dose of study drug
6. Histologically or cytologically proven diagnosis of pancreatic ductal adenocarcinoma (PDAC)
7. Locally advanced pancreatic cancer considered unresectable according to NCCN Guidelines® Version 2.2018 as determined by central imaging
8. Measurable disease as defined by Response Evaluation Criteria in Solid Tumors RECIST 1.1 criteria as determined by central imaging
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
10. Adequate liver function:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 x upper limit of normal (ULN),
    - Bilirubin ≤ 1.5 x ULN or in subjects with biliary stenting ≤ 2.0 x ULN
    - Alkaline phosphatase < 2.5 x ULN
    - Patients with elevated alkaline phosphatase, total bilirubin, AST and ALT, who have subsequently undergone biliary stenting and their liver tests are improving, do not need to wait for their alkaline phosphatase to become < 2.5x ULN if their total bilirubin, AST and ALT have improved to within required study levels and the alkaline phosphatase is decreasing.
11. Adequate bone marrow function: platelets >100,000 cells/mm3, hemoglobin > 9.0 g/dl and absolute neutrophil count (ANC) >1,500 cells/mm3
12. Adequate renal function: creatinine < 1.5 x ULN, creatinine clearance ≥ 30 mL/min
13. Less than grade 2 pre-existing peripheral neuropathy (per CTCAE)

5.2. Subject Exclusion Criteria

Subjects will be ineligible for and excluded from this trial if any of the following apply:

1. Prior chemotherapy or radiation for pancreatic cancer
2. Previous (within the past 3 years) or concurrent malignancy diagnosis except non-melanoma skin cancer and in situ carcinomas (excluding in situ breast cancer)
3. Major surgery within 4 weeks prior to signing informed consent form. Biliary stents are permitted.
4. History of allergy or hypersensitivity to human, humanized or chimeric monoclonal antibodies.
5. History of allergy or hypersensitivity to any of the chemotherapy agents being prescribed or their excipients
6. Any medical or surgical condition that may place the subject at increased risk while on study
7. Any condition potentially decreasing compliance to study procedures
8. Exposure to another investigational drug within 28 days of first dosing visit, or 5 half-lives of the investigational drug (whichever is longer)
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active systemic infections, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
10. Documented history of drug or alcohol abuse within 6 months of signing informed consent
11. Any medical condition that, in the opinion of the investigator, may pose a safety risk to a subject in this trial, may confound the assessment of safety and efficacy, or may interfere with study participation
12. Subjects with a history of; interstitial pulmonary disease, HCV, HBV or HIV infection
13. Subjects who have been administered a live vaccine within four weeks prior to the first administration of therapy
14. Subjects who cannot stop chronic medications that inhibit or induce CYP2C8 or CYP3A4
15. Subjects with poorly controlled comorbid conditions, including; congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), uncontrolled diabetes mellitus (DM) or neurologic disorders (not acutely related to pancreatic cancer) or limited function

5.3. Subject Withdrawal Criteria

Subjects may choose to withdraw from study treatment at any time.

5.3.1. Withdrawal Criteria from Neoadjuvant Treatment Period

Reasons a subject will be discontinued from study treatment include the following:

- Progressive Disease
- Adverse Event
- Lost to Follow-Up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Major protocol deviation that substantially affects subject safety or assessment of efficacy endpoints
- Withdrawal of Consent

Discontinued subjects should be evaluated in the clinic for EOT visit, followed for safety and continue in the Follow-up period.

A subject that meets the Treatment Compliance requirements (i.e. receives at least 11 of 13 planned doses of pamrevlumab or placebo, receives at least one dose of pamrevlumab or placebo in each cycle) and has no withdrawal of treatment due to AE or other reasons will be considered as having completed the study treatment.

5.3.2. Withdrawal Criteria for Follow-up Period

Reasons a subject will be discontinued from the study follow-up period include the following:

- Lost to Follow-up
- Withdrawal of Consent

A subject who dies during follow-up (or at any time during the trial) is considered as having completed the trial.

5.4. Replacement of Study Subjects

Subjects will not be replaced in this study.

5.5. Study Termination

FibroGen reserves the right to close any investigational site(s) or terminate the study at any time for any reason. Reasons for the closure of the study site or termination of a study by FibroGen may include (but are not limited to):

- Successful completion of the study at the investigational site
- Failure of the Investigator to comply with the protocol, GCP guidelines or local requirements
- Safety concerns
- Inadequate recruitment of subjects by the Investigator

6. TREATMENT OF SUBJECTS

6.1. Study Treatment

Study treatment is administered over a 28-day cycle, for up to six cycles. If dosing delays occur due to AEs or scheduling conflicts, for example, it is acceptable to extend a single treatment cycle to a total of 42 days and the neoadjuvant treatment period by an additional 6 weeks. Therefore, the total duration of the neoadjuvant treatment period could be approximately 24-30 weeks.

Information regarding storage, handling, preparation and administration of pamrevlumab can be found in the FG-3019 Investigator's Brochure and the study IP Manual. This information for the chemotherapy agents, gemcitabine, nab-paclitaxel and FOLFIRINOX, can be found in the package inserts for the products.

6.1.1. Pamrevlumab (FG-3019) or Placebo

The dose, route, infusion rate and schedule for the administration of pamrevlumab is provided in Table 1.

Table 1: FG-3019 (or Placebo): Dose, Route, and Administration

Agent	Dose	Route	Frequency	Infusion Rate
FG-3019 (or matching placebo)	35 mg/kg	IV	Day 1 and 15 of each cycle, with an additional dose on Day 8 of Cycle 1 only	Infuse over 1-hour (± 15 minutes) after completion of chemotherapy infusions

Note: DO NOT ADMINSITER FG-3019 AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.

Dosing for pamrevlumab (or placebo) will be based on the weight obtained on Day 1 of each dosing Cycle (i.e. Cycle 1 Day 1, Cycle 2 Day 1, etc). The total dose of pamrevlumab (or placebo) is not to exceed 4.1g. Subjects weighing more than 117kg will receive the maximum allowable dose of 4.1g. The volume of fluid infused must not exceed 410mL.

If split visit scheduling is implemented, the subject may be scheduled for a visit one day prior to dosing to complete study procedures per SOA. In these instances, it is acceptable to use the weight collected the day prior to dosing to calculate the dose.

6.1.2. Gemcitabine and Nab-paclitaxel

The dose, route, and schedule for administration of gemcitabine and nab-paclitaxel used in both treatment arms is provided in Table 2.

Table 2: Gemcitabine and Nab-paclitaxel: Dose, Route and Administration

Regimen Description				
Agent	**Dose**	**Route**	**Frequency**	**Infusion Rate**
Nab-paclitaxel	125 mg/m^2	IV	Days 1, 8, 15	IV over 30 minutes
Gemcitabine	1000 mg/m^2	IV, following nab-paclitaxel	Days 1, 8, 15	IV over 30 minutes

6.1.3. FOLFIRINOX

The dose, route and schedule for administration of FOLFIRINOX used in both treatment arms is provided in Table 3. The regimen below represents full dose FOLFIRINOX. Modified FOLFIRINOX (mFOLFIRINOX) may be administered at the investigator's discretion. Typically, for mFOLFIRINOX, the Irinotecan dose is reduced by 25% and the fluorouracil bolus dose is reduced by 20%. This mFOLFIRINOX regimen has been associated with good tolerability and comparable efficacy when compared to the full dose (Cavanna et al 2019). Investigators may also administer a mFOLFIRINOX regimen per their institutional guidelines. The different chemotherapy agents used in the FOLFIRINOX regimen are administered in the order listed below.

Table 3: FOLFIRINOX: Dose, Route and Administration

Regimen Description				
Agent	**Dose**	**Route**	**Frequency**	**Infusion Rate**
Oxaliplatin	85 mg/m^2	IV	Days 1 and 15 of each 28-day cycle	IV over 2 hours (±30 mins)
Folinic Acid or Leucovorin	400 mg/m^2	IV	Days 1 and 15 of each 28-day cycle	IV over 2 hours (±30 mins)
Irinotecan*	180 mg/m^2	IV	Days 1 and 15 of each 28-day cycle	IV over 90 mins (±15 mins) (may begin 30 minutes into Folinic Acid infusion)
Fluorouracil*	400 mg/m^2	IV	Days 1 and 15 of each 28-day cycle	IV administered bolus infusion
Fluorouracil	2400 mg/m^2	IV	Days 1-3 and Days 15-17 of each 28-day cycle	IV continuous infusion of 46 hours (±30 mins)

*NOTE: mFOLFIRINOX may be administered at the investigator's discretion and per their institutional guidelines.

6.1.4. Dose Schedules and Modifications

If, for administrative reasons, treatment cannot be administered on the planned visit date, dosing may be administered plus or minus 2 days from the scheduled visit date per protocol. Additional, guidance on dose omissions or delays is outlined in the section below.

Study treatments must be infused in the following order:

1. Nab-paclitaxel (chemotherapy agent)
2. Gemcitabine (chemotherapy agent)
3. Pamrevlumab or Placebo

OR

1. FOLFIRINOX (chemotherapy agents)
2. Pamrevlumab or Placebo

It is only permitted for subjects to receive pamrevlumab or placebo in combination with ONE chemotherapy treatment regimen during the neoadjuvant treatment period. It is not permitted to begin the trial on one chemotherapy regimen and switch to another before End of Treatment (i.e. in combination with pamrevlumab or placebo).

6.1.4.1. Dose Omissions and Modified Schedules (Gemcitabine plus Nab-paclitaxel)

Day 1 Dose

If both chemotherapy agents (G + NP) are held on Day 1 of the cycle, dosing with pamrevlumab or placebo should be delayed. The cycle will not be considered to start until the day the study treatment is actually administered to the subject (ie, 1-2-3-Rest, X-1-2-3-Rest, 1-2-3-Rest, etc). If only one chemotherapy agent is held (G or NP) on Day 1, dosing with pamrevlumab or placebo should be administered.

Day 8 Dose

In Cycle 1, if one or both chemotherapy agents are held on Day 8, dosing with pamrevlumab or placebo should continue on schedule. The Day 8 visit may also be delayed and given in combination with chemotherapy if the investigator feels the subject will be able to tolerate chemotherapy treatment at a later date. Any delay of more than two weeks should be discussed with the medical monitor. In all subsequent cycles (2-6), dosing with pamrevlumab or placebo does not occur on Day 8 visit so the cycle continues per protocol with one dose of chemotherapy not given/missed (ie, 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest).

Day 15 Dose

If chemotherapy agents are held or missed on Day 15 of the cycle, dosing with pamrevlumab or placebo should continue on schedule followed by a week of rest to complete the 28-day cycle if the investigator feels this is safe and in the subject's best interest. However, the Day 15 visit may also be delayed and given in combination with chemotherapy if the investigator feels the subject will be able to tolerate chemotherapy treatment at a later date. Any delay of more than two weeks should be discussed with the medical monitor.

If all chemotherapy agents are withdrawn (permanently discontinued), dosing with pamrevlumab or placebo must also be withdrawn. Subjects will be discontinued from study treatment and continue in the Follow-up Period.

6.1.4.2. Dose Omissions and Modified Schedules (FOLFIRINOX)

Day 1 Dose

If all chemotherapy agents are held or missed on Day 1 of the cycle, dosing with pamrevlumab or placebo should be delayed. The cycle will not be considered to start until the day the dose is actually administered to the subject (ie, 1-2-3-Rest, X-1-2-3-Rest, 1-2-3-Rest, etc). If only some chemotherapy agents are held on Day 1, dosing with pamrevlumab or placebo should be administered.

Day 8 Dose (Cycle 1 only)

Pamrevlumab or placebo is administered on Day 8 of Cycle 1 only. Delays to the Day 8 dose in Cycle 1 should be discussed with the medical monitor.

Day 15 Dose

If chemotherapy agents are held or missed on Day 15 of the cycle, dosing with pamrevlumab or placebo should continue on schedule followed by a week of rest to complete the 28-day cycle if the investigator feels this is safe and in the subject's best interest. However, the Day 15 visit may also be delayed and given in combination with chemotherapy if the investigator feels the subject will be able to tolerate chemotherapy treatment at a later date. Any delay of more than two weeks should be discussed with the medical monitor.

If all chemotherapy agents are withdrawn (permanently discontinued), dosing with pamrevlumab or placebo must also be withdrawn. Subjects will be discontinued from study treatment and continue in the Follow-up Period.

6.1.4.3. Dose Modifications

It is the Investigator's responsibility to modify the doses of gemcitabine and/or nab-paclitaxel in accordance with the product package insert guidelines for managing toxicities.

It is the Investigator's responsibility to modify the doses of FOLFIRINOX or mFOLFIRINOX in accordance with local or institutional guidance for managing toxicities.

Chemotherapy doses may be further modified, withheld or withdrawn at the investigator's discretion in the interest of subject safety and tolerability.

Dose modifications for pamrevlumab are not allowed. However, if an infusion reaction is suspected the infusion may be slowed, temporarily stopped or completely stopped before the full dose is administered (see Section 6.2.6 for details).

6.1.5. Treatment Compliance

All treatments are administered at the investigational site by qualified personnel and documented in the corresponding case report form (CRF).

Subjects must receive at least 11 doses of pamrevlumab or placebo to be considered as having completed all treatment cycles. Only one dose of pamrevlumab/placebo may be omitted per treatment cycle and no more than two doses total for a subject to be considered compliant and as having completed all cycles of treatment. If two consecutive doses of pamrevlumab/placebo are omitted or more than two doses total within the treatment period are omitted for a subject, they will be considered as having not completed all cycles of treatment due to non-compliance with

study drug. Delays of more than 2 weeks or interruptions (missed doses) that exceed two consecutive doses should be discussed with the medical monitor.

6.1.6. Concomitant Medications

6.1.6.1. Permitted Concomitant Medications

Regular supportive care as clinically indicated is permitted during this trial.

6.1.6.1.1. COVID-19 Vaccines

FibroGen recommends a time separation between the administration of a COVID-19 vaccine and blinded study drug (pamrevlumab or placebo) of at least 48 hours. While there are not safety concerns anticipated with the co-administration of pamrevlumab and COVID-19 vaccines, the time separation may allow for better interpretation of any adverse events and their relationship to the vaccine or study drug.

6.1.6.2. Prohibited Concomitant Medications

Pamrevlumab should not be administered to subjects with a history of allergic or anaphylactic reaction to human, humanized, or chimeric monoclonal antibodies.

Gemcitabine, nab-paclitaxel or FOLFIRINOX agents should not be administered to subjects with a history of allergy or hypersensitivity to these products or their excipients.

Radiation therapy and/or chemotherapy other than that prescribed per protocol is not allowed during the neoadjuvant treatment period and prior to surgical exploration.

Certain drugs that inhibit or induce CYP3A4 or CYP2C8 should be used with caution during study therapy administration. Specifically those outlined below:

CYP2C8 and CYP3A4 Inhibitors
Ketoconazole
Imidazole antifungals
Erythromycin
Fluoxetine
Gemfibrozil
Clopidogrel
Cimetidine
Ritonavir
Saquinavir
Indinavir
Nelfinavir

CYP2C8 and CYP3A4 Inducers
Rifampicin
Carbamazepine
Phenytoin
Efavirenz
Nevirapine

If a subject is taking a CYP2C8 or CYP3A4 inhibitor or inducer listed above as a chronic medication (i.e. long term use to manage an element of their medical history) at the time they are being screened for the trial and they cannot switch to a different medication, they should be excluded from the trial. Additionally, the use of the CYP inhibitors an inducers listed above should be avoided and only used with caution during the study for all patients receiving treatment with Nab-paclitaxel or FOLFIRINOX.

Live vaccines are prohibited for subjects receiving the G/NP or FOLFIRINOX chemotherapy regimen during study therapy administration and for 3 months after the last dose of study therapy.

Interactions between the gemcitabine, nab-paclitaxel or FOLFIRINOX and concomitant medications are described in their respective package inserts.

With regards to restrictions or recommendations related to chemotherapy agents, the sponsor's expectation and guidance is that each site follow the product label over the protocol as labels can vary by product, country, manufacturer, etc. and offer the most up to date guidance for investigators to safely manage the treatment of their patients.

6.1.6.3. Contraception Requirements

A non-clinical study evaluating the potential effects of pamrevlumab on embryo-fetal development has not been conducted. No adverse effects of pamrevlumab administration were observed in a study of rat male and female fertility. This study also includes treatment with chemotherapy agents which are potentially genotoxic.

Therefore, female subjects of childbearing potential are required to use highly effective contraception methods during the conduct of the study and for 6 months after the last dose of study drug.

Male subjects with partners of childbearing potential are required to use highly effective contraception methods during the conduct of the study and for 6 months after the last dose of study drug.

Investigators should counsel male subjects on the conservation of sperm prior to treatment due to the possibility of irreversible infertility/testicular damage due to the therapy with nab-paclitaxel and gemcitabine as noted in the SmPCs.

Additionally, investigators should counsel subjects on any additional contraceptive requirements outlined in the SmPCs for the prescribed chemotherapy agents.
A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. (CTGF, 2014)

6.2. Study Drug Materials and Management

This section of the protocol provides information and instruction regarding pamrevlumab (or placebo). Similar information for the chemotherapy agents can be found in the package inserts for those products. Additional details regarding study drug material and management can be found in the Study Investigational Product (IP) Manual.

6.2.1. FibroGen Investigational Product (Pamrevlumab) or Placebo

Pamrevlumab is a fully human IgG1 kappa monoclonal antibody that binds to CTGF and is formulated as solution for administration by IV infusion.

Matching placebo is formulated as solution to be administered in a manner that is identical to pamrevlumab infusion.

6.2.2. Formulation

Pamrevlumab is supplied in single-use glass vials containing either 10 mL or 50 mL of a sterile, preservative-free solution (100 mg pamrevlumab/vial or 500 mg pamrevlumab/vial, respectively). The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL L-histidine, 3.08 mg/mL L-histidine HCl, 8.01 mg/mL sodium chloride, and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0.

The placebo formulation is of identical composition as the pamrevlumab formation, except for the absence of pamrevlumab.

6.2.3. Study Drug Packaging and Labeling

Labels will be prepared and will comply with Good Manufacturing Practice and local regulatory guidelines.

6.2.4. Study Drug Storage

Vials of pamrevlumab and placebo must be stored refrigerated (2°C to 8°C), in a temperature-controlled and monitored environment, in the carton provided and protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation. Details regarding the reporting of temperature excursions can be found in the study IP Manual.

6.2.5. Study Drug Preparation

Pamrevlumab or placebo is infused undiluted after pooling the contents of the calculated number of vials in an empty infusion bag (total volume of fluid must not exceed 410 mL), according to the Dose Preparation Instructions in the Investigational Product (IP) Manual.

Once prepared, the IP infusion is stable at room temperature for up to 6 hours. Otherwise, if prepared IP is not used immediately it should be stored and refrigerated at 2-8ºC (to prevent microbial growth, as it does not contain preservatives) and used within 48 hours or be discarded.

Pamrevlumab or placebo infusion solutions are administered by IV infusion, using an infusion set with a 0.2 μm in-line filter.

6.2.6. Study Drug Administration

Pamrevlumab/placebo infusion should be administered over 1 hour ± 15 minutes. Subjects should be carefully monitored for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. The post-infusion observation period may be reduced to 30 minutes if the subject has had no infusion-related AEs for three consecutive infusions. The IV access should remain in place and be maintained per site procedures until the end of this post treatment observation period. If a subject has an infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion reaction and continues pamrevlumab dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Pamrevlumab will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of pamrevlumab.

Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

6.2.7. Study Drug Handling and Disposal

All study drug provided by the Sponsor should be retained at the site until otherwise instructed in writing by the Sponsor (or designee). The Sponsor (or designee) will perform drug accountability and reconciliation for all study drug received at the site prior to approving study drug return/destruction. Upon completion of accountability/reconciliation or upon completion of the study or termination of the investigational site, all used, unused, partially used study drug, and all study drug that was not dispensed will be shipped to a destruction site designated by the Sponsor (or designee) for destruction. Study drug may be destroyed on site according to local/institutional policies by the pharmacy/authorized staff with approval from Sponsor (or designee). Please refer to the IP Returns Instruction Manual for additional information on study drug accountability.

7. ASSESSMENTS OF EFFICACY

7.1. Study Assessments

A signed and dated IRB/IEC-approved informed consent must be obtained before any study-specific assessments are performed. Assessments that are part of routine care are not considered study-specific and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study and randomized.

During the COVID-19 global pandemic, all sites were approved to conduct study assessments (i.e. physical exams, AE/CM review, etc) via telehealth visits if this was the only feasible option available.

7.1.1. Screening Period

All screening procedures must be performed within 30 days of Cycle 1 Day 1. Study procedures to be performed during the screening period can be found in the Schedule of Assessments (Appendix 1). In order to avoid unnecessarily repeating study screening procedures (i.e. CT scans that would increase radiation exposure risk, delays due to COVID, etc) short extensions (up to 14 days maximum) to the screening window may be granted with prior approval from the Medical Monitor.

Sites must confirm that all inclusion criteria (see Section 5.1) have been met and no exclusion criteria (see Section 5.2) have been met prior to making a request for randomization. A diagnostic biopsy is required for histological confirmation of pancreatic ductal adenocarcinoma (PDAC). Central laboratory samples will be collected and the results will be used to determine eligibility. CT scans will be sent to the central review board for evaluation to confirm subjects have locally advanced unresectable disease. If the site has performed additional staging procedures per SOC (i.e. laparoscopy or staging MRI) that indicate metastatic disease, these results may also be considered by the site in the final determination of eligibility.

All subjects will be entered in IXRS and those who are eligible for participation will be randomized in the trial. All randomized subjects will be entered in the clinical database (EDC).

7.1.1.1. Role of Central Review in Determining Eligibility for Participation and Defining Stratification Factors

A central review board (to include radiologists and surgeons) will confirm subjects have locally advanced unresectable disease prior to enrollment through a review of the CT scan (per RECIST 1.1 and NCCN Version 2.2018) collected during screening. If available, any additional clinical data (i.e. MRIs, biopsy results, and historical CT scans) should be provided to the central review board at baseline as supplemental information to the central readers regarding any possible metastatic tumors on the screening scan. The results provided by the central review board will be used to determine eligibility.

The central review board will provide an assessment of SMA encasement and unreconstructible disease to the sites during screening to support stratification at randomization for any subjects determined to be eligible.

Process details surrounding the central review can be found in the Imaging Manual.

7.1.2. Neoadjuvant Treatment Period

All subjects will be treated with pamrevlumab or placebo in combination with gemcitabine and nab-paclitaxel or FOLFIRINOX for up to six 28-day cycles. Study procedures are described below and will be performed in accordance with the SOA (see Appendix 1). Subjects who complete study treatment will undergo evaluation to determine their eligibility for surgical exploration (see Section 4). CT scans will be performed approximately every 8 weeks and evaluated by central imaging until disease progression is noted. If disease progression is noted during the neoadjuvant treatment period, subjects will be discontinued from study treatment. Subjects who discontinue treatment early (see Section 5.3) will complete an EOT visit and continue in the follow-up period.

7.1.3. Safety Follow-up

All subjects enrolled will have a safety follow-up visit approximately 28 days after the last dose of study treatment and a final safety follow-up phone call approximately 60 days post last dose of study treatment. After the protocol-required reporting period (60 days after the last dose), the investigator does not need to actively monitor subjects for serious adverse events (SAEs). However, if the investigator becomes aware of a SAE that may be possibly related to study treatment after the protocol-required reporting period, the investigator may report the event to FibroGen as outlined in Section 8. SAEs reported outside of the protocol-required reporting period will be captured within the safety database only as clinical trial cases for the purposes of expedited reporting.

7.1.4. Determination of Eligibility for Surgical Exploration

To be considered eligible for surgical exploration, a subject must meet at least one of the four protocol-defined criteria and have no contraindication to surgery as outlined below:

The protocol-defined criteria for surgical eligibility are:

- Reduction in CA 19-9 level ≥ 50%
- FDG-PET SUVmax decrease by ≥ 30% at EOT when compared to baseline
- Partial response [PR], complete response [CR] or stable disease [SD] per RECIST 1.1 at EOT
- Resectable or borderline resectable per NCCN® Version 2.2018

Contraindications to surgical eligibility are:

- Development of distant metastases or local progression per RECIST 1.1
- Performance status of Karnofsky score ≤ 50
- Unreconstructible disease as determined by central radiological/surgical review
- Other conditions that are considered by the PI/surgeon to be contraindications to surgery

The central review board (to include radiologists, surgeons and oncologists) will review information provided by the site and determine whether a subject is eligible for surgical exploration per protocol. The PI/surgeon will ultimately decide whether a subject will undergo surgery. See Section 7.1.4.1 for details.

Subjects who do not undergo surgical exploration (e.g. subjects who did not complete study treatment, do not meet any of the protocol-defined criteria for surgical eligibility or have a contraindication to surgery at the time of evaluation) will continue in the Follow-up period.

All subjects who do undergo surgical exploration within the protocol specified window will be followed for surgical safety and outcomes.

7.1.4.1. Role of Central Review in Determination of Eligibility for Surgical Exploration

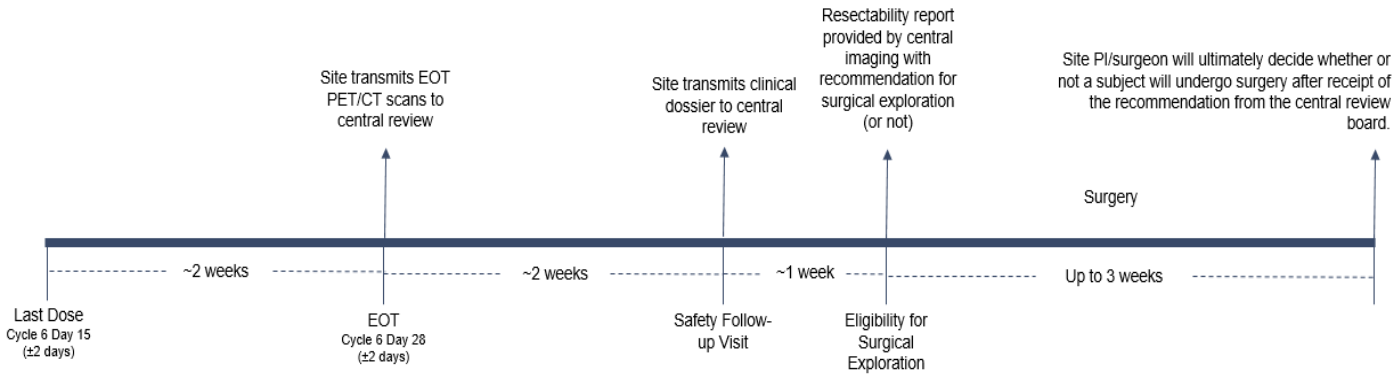
CT and PET scans collected at EOT will be evaluated by the central review board to confirm whether a subject has met the protocol-defined criteria for RECIST 1.1, SUVmax, NCCN Version 2.2018 criteria response and/or whether they have unreconstructible disease. The site will also provide the central review board with CA19-9 values to confirm response per the protocol defined criteria.

Additionally, the site will provide the central review board with required information for their assessment of the subject's performance status and a summary of existing conditions/contraindications following the Safety Follow-up Visit. Conditions that may be contraindications to surgery will be reported to the central review board through the Safety Follow-up visit. Medical co-morbidities that occur after the Safety Follow-up visit and preclude surgery will not be provided to the central review board, and therefore will not be considered in the determination of surgical eligibility, but will be considered by site in their decision making process regarding surgical exploration. These co-morbidities will be documented in the clinical database.

The central review board will provide their assessment of surgical eligibility to the site within 5 business days of receipt of all required information (approximately 1 week after the Safety Follow-up Visit). After the recommendation from the central review board is received at the site, the PI/surgeon will make the final decision as to whether or not a subject will undergo surgery. All instances of discordance between the determination of eligibility for surgical exploration by the central review board and the final action taken by the site with regards to surgical exploration will be documented in the clinical database.

Figure 2 provides an overview of the central review process. Details can be found in the Central Imaging Protocol and Study Reference Manual.

Figure 2: Central Review Schema for Determination of Eligibility for Surgical Exploration



[a]CT and PET scans collected at EOT will be provided to central review for evaluation of protocol defined surgical eligibility criteria and contraindications: RECIST response, NCCN status, PET SUVmax decline and unreconstructible disease
[b]Additional clinical information will be provided to central review for evaluation of protocol defined surgical eligibility criteria and contraindications: CA19-9 results, Karnofsky score and summary of existing medical conditions through the Safety Follow-up Visit.
[c]Per protocol, surgery will occur at least 4 weeks post last dose, after receipt of the recommendation from the central review board, and no longer than 8 weeks post last dose

7.1.5. Surgical Exploration/Surgical Resection

Surgery will occur at least 4 weeks after last dose (allowing for a wash-out period from treatment) and only after receipt of the recommendation from the central review board with regards to surgical eligibility.
An outcome of R0 or R1 will be considered a 'Resection Achieved' while an outcome of R2 or partial resection will be considered a 'Resection Not Achieved'. Final surgical outcomes (R0 and R1) for all 'Resection Achieved' subjects will be determined by the central pathology lab. The sponsor/sites remain blinded to the central pathology lab assessment until their final analysis.

If a subject undergoes surgical exploration, but the surgeon is unable to perform resection (e.g. due to identification of metastases or extensive vascular involvement), it will be considered a 'Resection Not Attempted'.

Surgery will be performed in accordance with institutional standards and SOPs. All surgeons performing surgery for this study will be trained on the protocol. All subjects who undergo surgical exploration within the protocol specified window will have tissue samples collected and sent to central pathology and will be followed for surgical complications for 90 days post discharge.

7.1.6. Follow-up Period

All subjects will be followed for disease progression (if not previously noted) or recurrence (local or distant) following resection, survival and any additional anti-cancer therapy received during the Follow-up period. Follow-up visits (telehealth visits or phone calls are acceptable) should occur approximately every 3 months post last dose.

For some subjects, CT scans may continue to be performed and submitted for central review during the follow-up period. For subjects who complete treatment without evidence of disease progression and do not undergo resection, CT scans will continue to be performed approximately

every 8 weeks (±14 days) and evaluated by central imaging until progression is detected (per RECIST 1.1). For subjects who undergo resection, follow-up CT scans to evaluate recurrence of disease will be evaluated by central imaging and performed approximately; every 4 months up to 2 years post-resection and every 6 months from 2 years to 5 years post-resection. The investigator may perform an "off schedule" CT scan at any time post resection if recurrence of disease is suspected clinically; these scans will be submitted to central imaging for review/confirmation of recurrence/disease progression. CT scans conducted post resection during the Follow-up Period may be performed within 1 month (i.e. ± 30 days) of the suggested intervals above.

All subjects will be followed for survival (until death) or until the last subject to complete treatment has been followed for approximately 18 months post-last dose (i.e. at this time it is expected that 233 death events will have occurred to support final analysis of OS). Subjects may receive second-line therapy at the investigator's discretion.

7.1.7. Missed Visits

Study treatment may be withheld/interrupted due to safety reasons, resulting in a "missed" visit. Study visits may be delayed for a total window not to exceed + 6 weeks over the course of the treatment period. Adjustments to the dosing schedule for pamrevlumab/placebo should be discussed with the study Medical Monitor as outlined in Section 6.1.3. If a visit is missed and not rescheduled, it will be captured accordingly in the clinical database.

7.1.8. Unscheduled Visits

Unscheduled visits/assessments may be required at the discretion of the investigator. Unscheduled visit data will be captured accordingly in the clinical database.

7.1.9. Early Withdrawal from Treatment

Subjects who prematurely discontinue treatment during the neoadjuvant treatment period should be strongly encouraged to complete the final efficacy evaluations scheduled for the EOT visit as specified in the SOA (Appendix 1). These subjects must be followed for safety for at least 60 days following their last dose of study drug. Discontinued subjects will continue in the Follow-up period and be followed for progression (if not previously noted), survival and additional anti-cancer therapies for pancreatic cancer.

7.2. Assessments

Refer to the Schedule of Assessments (Appendix 1 and 2) for details regarding the timing and frequency of study assessments.

7.2.1. Vital Signs (Including Weight and Height)

Vital signs to be collected include heart rate, blood pressure, respirations, temperature and weight:

- Heart rate should be collected as beats/min
- Systolic and diastolic blood pressure should be collected from subjects in seated position
- Respirations should be collected as breaths/min
- Temperature should be taken as oral or tympanic and captured as °F or °C
- Weight should be collected in lbs or kgs
- Height is collected during screening only.

7.2.2. Physical Exam

A full physical exam is required during screening and on Day 1 of each treatment cycle. All other physical exams may be abbreviated unless a full physical exam is warranted in the opinion of the investigator. A full physical exam may include, but is not limited to, review of the following systems:

- General Appearance, HEENT, Lungs, Heart, Chest & Back, Abdomen, Extremities, Neurologic, Skin

7.2.3. Electrocardiogram (ECG or EKG)

EKGs will be performed in accordance with institutional standards at screening, Day 1 of each Cycle and EOT.

7.2.4. Laboratory Evaluations

Details regarding sample collection, preparation and transport can be found in the central lab manual.

7.2.4.1. Central Laboratory Evaluations

The following labs will be evaluated by a central laboratory in accordance with the SOA (Appendix 1):

Table 3: Laboratory Tests

CBC:	**Chemistry Panel:**
Absolute neutrophil count (ANC)	Bicarbonate
Eosinophils	BUN
Erythrocyte count (RBC)	Calcium
Hematocrit	Creatinine
INR	Chloride
PTT/PT	Magnesium
Hemoglobin	Glucose
Leukocyte count (WBC)	ALP
Lymphocytes	ALT
Mean corpuscular volume	AST
Monocytes	Bilirubin, total
Neutrophils	Albumin
Platelets	Phosphorous
CRP	Potassium
Basophils	Sodium
Other: CA 19-9	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; INR = international normalized ratio, PT/PTT = prothrombin time/partial thromboplastin time; RBC = red blood cell; WBC = white blood cell.

Central lab results obtained during the screening period will be used to determine subject eligibility for participation in the trial. Central lab results will be reviewed by the investigator for clinical significance and to determine appropriate reporting of adverse events (see Section 8.3.7). Central lab results for CA19-9 will be used to determine eligibility for surgical exploration.

During screening, a serum pregnancy test will be performed by the central lab for any females of child-bearing potential (WOCBP). For WOCBP, serum or urine pregnancy tests should be performed approximately monthly thereafter at the site level per the SOA in Appendix 1.

Local lab results may be used to evaluate subject condition prior to dosing.

7.2.4.2. Local Laboratory Evaluations

Whenever possible, and as outlined above, central lab samples should be collected/used for the purposes of this trial. However, during the COVID-19 global pandemic, all sites were approved to use local labs if it was not possible to collect/use central labs (i.e. due to local/site restrictions or due to lab kit shortages). Any instance in which local labs were used will be documented in the clinical database and local lab results will be captured. Sites using local labs must submit their local lab ranges for reference.

7.2.4.3. Pharmacokinetics and Pharmacodynamics

Additional samples will be collected to evaluate PK, HAHA, HAHA-NA and CTGF in accordance with the SOA in Appendix 1. The central laboratory will manage the storage of these samples while analysis will be performed at the specialty lab specified in the central lab manual.

7.2.4.3.1. Pharmacokinetics

Plasma samples will be collected in all subjects for evaluation of C_{max} and C_{min} trough levels of pamrevlumab (FG-3019) according to the SOA in Appendix 2. A central laboratory will measure plasma FG-3019 levels using a validated assay. For the analysis of C_{max} and C_{min} data, it is critical to accurately record the dosing time and date in addition to the sampling collection time and date.

7.2.4.3.2. Human Anti-Human Antibodies (HAHA) and Connective Tissue Growth Factor (CTGF)

Plasma samples will be collected for evaluation of human anti-human antibodies (HAHA) and connective tissue growth factor (CTGF) in all subjects according to the SOA in Appendix 1. Central laboratories will measure HAHA and CTGF level using validated assays.

HAHA-NA samples will be collected from all subjects at the Safety Follow-up visit. These samples will undergo evaluation for neutralizing antibodies for all samples/subjects with positive/specific HAHA results. The prevalence and duration of binding and neutralizing antibodies and the effect of these antibodies on the pharmacokinetics, pharmacodynamics markers, efficacy, and safety of pamrevlumab will be assessed.

7.2.4.3.3. Pharmacodynamics and Biomarkers (Blood and Tumor Tissue)

Tumor tissue will be collected from all resected subjects for histological analysis and examination of nucleic acids. Plasma samples will be collected from all subjects according to the SOA in Appendix 1 to support the exploratory analysis of protein and nucleic acid markers. Final decisions about the specific markers to be evaluated in tumor tissue or plasma samples collected for exploratory analysis will be made at the time of analysis and will be based on the review of medical literature, additional data regarding FG-3019's mechanism of action, preliminary results and availability of material for assay. Details regarding the collection and storage of tumor tissue will be outlined in the Central Pathology Manual.

7.2.5. Performance Status

7.2.5.1. Eastern Cooperative Oncology Group (ECOG)

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, to assess how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis (Oken, 1982). The ECOG performance scale will be used to evaluate subject's performance status during screening and throughout the trial. See Appendix 1.

7.2.5.2. Karnofsky Performance Scale Index

The Karnofsky Performance Scale Index is an assessment tool for functional impairment (Appendix 3). It can be used to assess the prognosis in individual patients. In most serious illnesses, the lower the Karnofsky score, the worse the likelihood of survival (Boeck, 2007). The Karnofsky performance scale will be used to evaluate subject's performance at EOT only. Karnofsky performance scores will be evaluated by the central review team in determination of eligibility for surgical exploration per protocol.

7.2.6. Carbohydrate Antigen 19-9 (CA 19-9)

CA 19-9 is a tumor marker that is used primarily in the management of pancreatic cancer (Poruk, 2013). CA 19-9 levels will be measured at baseline and regularly throughout the study. CA 19-9 results will be evaluated by the central laboratory. CA19-9 results will be evaluated by the central review team in determination of eligibility for surgical exploration per protocol.

7.2.7. Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) Scan

Studies have shown FDG-PET may be useful in treatment response assessment and may have potential in guiding the management of patients with PDAC (Yeh, 2018). An FDG-PET scan will be performed at baseline and EOT to evaluate SUVmax and metabolic tumor volume in the primary pancreatic tumor. If a subject discontinues treatment early, an EOT PET scan is required unless the baseline PET was performed less than 8 weeks from EOT. All PET scans will be performed and evaluated in accordance with the central imaging protocol. PET scans will be evaluated by the central review team in determination of eligibility for surgical exploration per protocol.

7.2.8. Computer Tomography (CT) Scan

CT scans will be performed using pancreatic protocols and in accordance with the central imaging charter until progression. Central imaging will conduct RECIST reads on all CT scans collected during screening, the neoadjuvant treatment period and follow-up as outlined in the SOA (Appendix 1).

Baseline CT scans (collected during the screening period) will be evaluated by the central radiological/surgical review team to confirm subjects have locally advanced, unresectable disease prior to enrollment. Central radiological/surgical review team will also review each subjects' baseline CT scan to determine the degree of SMA encasement and whether or not they have unreconstructible disease for the purposes of stratification at randomization.

All CT scans collected during the study will be evaluated by the central review team for progression per RECIST until progression is noted. EOT CTs, for subjects who complete all 6 cycles of treatment, will be evaluated at EOT by the central review team in determination of eligibility for surgical exploration per protocol.

If a subject cannot tolerate a contrast CT or other reasons, MRIs may be performed. If MRIs are performed during screening or the neoadjuvant treatment period due to contrast intolerance or other reasons, they will be sent to central imaging for review.

7.2.9. Patient Reported Outcomes (PROs)

Patient reported outcome (PRO) data will be collected in all subjects to evaluate the most important patient reported symptoms, treatment related symptoms and functional impacts that may be responsive to treatment. EORTC-QLQ-C30 and PRO CTCAE™ questionnaires will be administered as specified in the SOA (prior to dosing in all applicable instances) (see Appendix 1).

At the study outset, all PRO data was being captured as direct entry by the subject via electronic device (ePRO). During the COVID-19 global pandemic, all sites were approved to use paper versions of the PRO/QOL questionnaires. Use of paper questionnaires will be documented and the results will be transcribed into the clinical database.

7.2.9.1. EORTC-QLQ-C30

EORTC QLQ-C30 is a health related quality of life questionnaire (HRQOL) developed to assess the quality of life of cancer patients. EORTC QLQ-C30 Version 3.0 is the most recent version and will be used for this study. This questionnaire will be collected on Day 1 of each treatment cycle (prior to dosing), at EOT and the Safety Follow-up visit.

7.2.9.2. PRO-CTCAE™

The following symptoms from the PRO-CTCAE™ library will be included in a symptom specific patient questionnaire: decreased appetite, nausea, vomiting, diarrhea, abdominal pain and fatigue. This questionnaire will be collected on Days 1, 8 and 15 in the first three treatment cycles (Cycles 1-3), on Days 1 and 15 in the last three treatment cycles (Cycles 4-6) and at the EOT and Safety Follow-up Visit.

7.2.10. Surgical Outcomes and Complications

All subjects that undergo surgery within the protocol specified window (at least 4 weeks after the last dose and no longer than 8 weeks after the last dose) will be followed for surgical outcomes and complications for 90 days after their discharge. Surgical safety will be assessed by the collection of surgical outcomes measures and surgical complications that occur during this timeframe.

7.2.10.1. Surgical Complications

All surgical complications that occur will be collected and graded in severity according to the Clavien-Dindo Classification (Appendix 4).

7.2.10.2. Surgical Outcomes

The following surgical outcomes will be measured:

- Type of procedure/resection
- Resection outcome
- >10 lymph nodes
- Operative time >10 hours
- Length of hospital stay
- Estimated blood loss (EBL) at time of surgery
- Transfusions; units of blood
- Return to operating room within 30 days

8. ASSESSMENTS OF SAFETY

8.1. Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the study drug.

8.2. Definitions

8.2.1. Definition of an Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject as defined in the study protocol are recorded in the subject's medical record. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches and gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective surgery or a medical procedure while on study, is not considered an adverse event. (Section 8.3.1).

8.2.2. Definition of a Serious Adverse Event (SAE)

A serious adverse event is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the primary cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled or pre-planned hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures (including elective procedures) do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1. Adverse Event Reporting Period

The safety reporting period begins after the subject has signed the informed consent and ends 60 days after the last dose of study drug. Only SAEs need to be reported following consent and prior to first dose. While both AEs and SAEs need to be reported from first dose through 60 days post last dose. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5). Pregnancy reporting requirements are outlined in Section 8.3.6.

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2. Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will actively seek information from each subject at each visit to collect any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the baseline or previous visit, but shall not be specifically solicited. There will be no directed questioning or solicitation for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff. The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. The investigator is expected to follow reported adverse events until stabilization or reversibility.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3. Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 5.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild:** Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death**: Fatal AE.

8.3.4. Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile of study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- Related:
  - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re- occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- Not Related:
  - The event represents a pre-existing underlying disease that has not worsened on study
  - The event has the same characteristics of a known side-effect associated with a co-medication
  - The event is an anticipated medical condition of anticipated severity for the study population
  - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5. Reporting Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent/assent through 60 days after the last dose of pamrevlumab are recorded in the subject's medical record and are submitted to FibroGen. All SAEs must be submitted to FibroGen within 24 hours following the investigator's knowledge of the event via the SAE report form. Additionally, pamrevlumab related SAEs (including deaths) that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

If a subject is permanently withdrawn from protocol required therapies because of a serious adverse event, this information must be submitted to FibroGen. FibroGen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and central IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to FibroGen. In some countries (e.g. European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to FibroGen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting; these cases will not be included in the clinical study report.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

8.3.5.1. Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2. Deaths

The investigator will report the fatal event to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to 60 days after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. If the investigator becomes aware of a death occurring after the AE reporting period and considers it related to study drug, it will be reported as an SAE.

8.3.6. Pregnancies: Reporting and Follow-up of Subjects and Female Partners of Subjects

The outcome of all pregnancies for a female study participant or female partners of a male study participant should be followed up and documented as described. If a female subject or a partner of a male subject becomes pregnant while the subject is receiving study treatment or within 6 months after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a

Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

Pregnancy itself is not an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Pregnancies are followed up to outcome even if the subject was discontinued from the study. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

If a lactation case occurs while the female subject is taking protocol-required therapies or within 60 days after the last dose of study treatment, report the lactation case to FibroGen. In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 6 months after the last dose of pamrevlumab. Any lactation case should be reported to FibroGen's Safety within 24 hours of the investigator's knowledge of event.

8.3.7. Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all results provided by the central laboratory throughout the study in a timely manner, and determine whether any abnormal laboratory values are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

Clinically significant laboratory abnormalities will be reported as AEs. If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

8.3.8. Disease Progression

Disease progression assessed by radiographs or other methods should not be reported as an adverse event, unless the outcome is fatal during the safety reporting period. Deaths related to progression of the underlying disease outside of the safety reporting period should be recorded on the corresponding page of the CRF (unless the patient has withdrawn consent).

8.3.9. Special Reporting Situations

Special reporting situations include:

- Overdose (any dose greater than 4.1g)
- Suspected abuse/misuse
- Inadvertent or accidental exposure
- Medication error (e.g. incorrect dose administered)
- Drug-drug interactions

Report special situations to FibroGen Safety within 24 hours of the investigator's knowledge of the event. See Study Reference Manual for detailed reporting instructions.

8.3.10. Safety Monitoring

8.3.10.1. Data Monitoring Committee (DMC)

In addition to routine safety monitoring, an independent Data Monitoring Committee (DMC) will be established to review safety data on an ongoing basis. A DMC charter will establish the procedures, meeting frequency, and scope of responsibilities of the committee. The DMC will be comprised of individuals with relevant expertise who are external to the study and are not directly involved with the study conduct.

The sponsor proposes to convene the DMC within 21 days after the first 10 subjects have received at least 3 cycles of investigational drug in combination with the FOLFIRINOX regimen to specifically evaluate the safety of this combination. After this initial DMC meeting and if no additional signal has been identified in addition to what is seen with FOLFIRINOX, the DMC will meet approximately every 6 months during the study, in accordance with the DMC Charter.

9. STATISTICS

9.1. Sample Size Determination

The study is planned to enroll approximately 280 subjects. All subjects will be prescribed either gemcitabine plus nab-paclitaxel (G/NP) or FOLFIRINOX prior to randomization, and then will be randomized with 1:1 randomization ratio to the addition of either pamrevlumab or placebo.

This sample size is estimated based on the assumption that the median OS for the pamrevlumab arm and the placebo arm is 24 and 16.3 months, respectively. The assumptions of overall survival are based on the FGCL-3019-069 study results for G/NP + pamrevlumab and G/NP alone. This improvement represents a hazard ratio (HR) of 0.68. With this HR, 233 deaths will provide at least 80% power when using a test statistics with a 2-sided significance level of 5%. With the enrollment of approximately 280 subjects, 233 deaths are estimated by the end of the follow-up period.

If the treatment effect on EFS has a hazard ratio 0.60, then 161 events would be required to provide 75% power when using a stratified log-rank statistic with (one-sided) 0.005 false positive error rate.

For the assessment of OS, all patients will be followed for approximately 18 months after the last subject enrolled completes treatment which will occur about 48 months after the start of the trial, to achieve 233 events, (i.e., deaths). With 233 events, the trial would have at least 80% power to detect a hazard ratio of 0.68, when using a stratified log-rank statistic having (two-sided) significance level of 5%.

9.2. Analysis Populations

9.2.1. Intent to Treat (ITT) Population

The ITT Population is defined as all randomized subjects regardless of whether or not study treatment is received. The primary analysis of efficacy will be based on the ITT population. Subjects will be analyzed according to the treatment randomized.

9.2.2. Per Protocol (PP) Population

The Per Protocol (PP) Population is defined as all subjects who have completed the 6-cycle study treatment, had baseline and at least one post-baseline tumor assessment.

9.2.3. Safety Population

The Safety Population is defined as all randomized subjects who have received study medication. The primary analysis of safety will be based on the Safety population. Subjects will be analyzed according to the treatment received.

9.3. Statistical Analysis

9.3.1. General Considerations

After approximately 233 deaths are reached, the final analysis for the primary endpoint and secondary endpoints will be conducted. A gate-keeping strategy will be employed to ensure overall control of the type I error rate. The secondary efficacy hypotheses will be relevant only if the primary efficacy null hypothesis is first rejected.

Following the rejection of the primary efficacy null hypothesis, each secondary hypothesis will be tested. Each treatment effect testing will be relevant only if the preceding tests have been rejected at the same 5% level of significance (two-sided) as for the primary endpoint. The testing order for the secondary endpoints is as the order listed in section 3.2.3 of the protocol.

A hierarchical approach will be implemented. If the analysis of the effect of pamrevlumab on EFS is statistically significant at two-sided p=0.01, then that alpha will be carried forward to the final analysis of OS, which then would be conducted at the two-sided p=0.05 level. If the effect of pamrevlumab on EFS is not statistically significant at two-sided p=0.01, then the final analysis of pamrevlumab's effect on OS would be conducted at the two-sided p=0.04 level.

When the interim analysis of EFS is conducted (i.e. when approximately 161events have occurred), an interim look of OS will also be conducted at that time by the DMC for lack of benefit analysis. The final analysis of OS will occur when 233 OS events have occurred, which is estimated to occur approximately 48 months into the trial.

The sponsor likely will pursue a regulatory submission for an accelerated approval if the effect of pamrevlumab on EFS at the interim analysis is statistically significant at two-sided p=0.01.

After the interim analysis, to protect the integrity of the OS data for the final analysis, confidentiality of the emerging OS data will be maintained (Fleming 2018).

A Data Access Plan describes the strategy for maintaining confidentiality of the emerging OS data until final database lock of the FGCL-3019-087 trial.

9.3.2. Subject Enrollment and Disposition

The number (%) of subjects who completed or discontinued the study and reasons for early discontinuation will be summarized by treatment for subjects in the ITT population.

9.3.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for subjects in the ITT population.

9.3.4. Efficacy Analyses

9.3.4.1. Analysis of Overall Survival (Primary Endpoint)

Overall survival (OS) is defined as the time from randomization until death from any cause and is measured in the intent-to-treat population.

For subjects who are alive at data cut or at study closure, the recorded date of last known alive, last contact date, or the date of the last clinic visit is defined as the censoring date for OS.

The OS will be summarized using the Kaplan-Meier method. The Cox proportional hazard model including treatment and stratification factors: chemotherapy treatment regimen, SMA encasement, unreconstructible disease and geographic region, will be used to compare the 2 treatment arms and to estimate the hazard ratio and the corresponding 95% confidence interval.

9.3.4.2. Analysis of Event-free Survival (EFS) (Surrogate Endpoint for Accelerated Approval)

The EFS endpoint would be a composite time-to-event endpoint, the event being 'treatment failure' defined as the earliest occurrence of:

a) Failure to achieve disease-free status locally after completion of neoadjuvant treatment and/or after surgery (i.e., resection failure or progression that precludes surgery); or

b) Local or distant recurrence; or

c) Death

For subjects who did not have the event at data cut or at study closure, the latest date of the following events will be defined as the censoring date: last post-baseline CT, last post-baseline PET scan, the last known record of 'Not progressed', surgical exploration, date of surgery cancellation. EFS will be summarized using the Kaplan-Meier method. The Cox proportional hazard model including treatment and stratification factors: chemotherapy treatment regimen, SMA encasement, unreconstructible disease and geographic region will be used to compare the treatment effect and to estimate the hazard ratio and corresponding 95% CI.

9.3.4.3. Analysis of Progression-free Survival (PFS)

PFS is defined as the time from randomization until disease progression or death, whichever occurs first (FDA Guidance, 2018).

For subjects who did not have progression at data cut or at study closure, the latest date of the following events will be defined as the censoring date: last post-baseline CT, last post-baseline PET scans, the last known record of 'Not Progressed'.

PFS will be summarized descriptively using the Kaplan-Meier method. The Cox proportional hazard model including treatment and stratification factors: chemotherapy treatment regimen, SMA encasement, unreconstructible disease and geographic region will be conducted to compare treatment effect and to estimate the hazard ratio and corresponding 95% CI.

9.3.4.4. Analysis of Best Overall Objective Response Rate (ORR)

Best overall objective response rate (ORR) is one of the secondary endpoints where objective response is defined as a complete response (CR) or partial response (PR) according to RECIST 1.1. Objective response will be based on the best overall response recorded from Day 1 until centrally-assessed progressive disease (PD), death, or first administration of anti-tumor treatment (other than study medication), whichever occurs first. Patients who receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

ORR will be summarized by using the analysis of the difference between two proportions for the ITT Population and PP Population. Normal approximation method will be used as the sample size is larger than 30. Estimation and 95% CI for the ORR for the two arms will be computed and difference of the two proportions and its 95% CI will be estimated by SAS PROC FREQ procedure. The p-value for testing the difference of the two proportions will be used for hypothesis testing for treatment comparison.

9.3.4.5. Analysis of Physical Functioning by EORTC-QLQ-C30

The physical functional scale will be scored according to the EORTC- QLQ-C30 scoring manual. For functional scale, the scoring will not be affected if there are at least half of the items from the scale answered. All the items that are completed will be used to calculate the raw score then through a linear transformation to a standardized score for the scale. The standardized score range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms. If there are more than half of the items from the scale that are missing, then the scale score at the visit will be set to missing.

Difference between treatment arms in mean change from baseline Physical Functional score at selected visits during the treatment period will be assessed using a MMRM model, with adjustment for randomization stratification factors. The unstructured covariance will be applied first. If the algorithm for unstructured covariance pattern does not converge then heterogeneous Toeplitz structure will be used. If this second model does not converge then the (homogeneous) Toeplitz structure will be tried, and if all of these covariance structures failed to converge then the compound symmetry will be used.

9.3.4.6. Analysis of Abdominal Pain and Fatigue Score by NCI-PRO-CTCAE

The abdominal pain and fatigue scales will be scored according to the scoring manual.

Difference between treatment arms in mean change from baseline of the abdominal pain and fatigue scores at selected visits during the treatment period will be assessed using a mixed effect model for repeated measurements (MMRM), with adjustment for randomization stratification factors.

The unstructured covariance will be applied first. If the algorithm for unstructured covariance pattern does not converge then heterogeneous Toeplitz structure will be used. If this second model does not converge then the (homogeneous) Toeplitz structure will be tried, and if all of these covariance structures failed to converge then the compound symmetry will be used.

9.3.5. Pharmacokinetic Analyses

The plasma concentrations of the PK samples will be determined by a validated assay, and a plan for population PK as well as exposure-response analysis will be provided.

9.3.6. Safety Analyses

Treatment-emergent adverse events (TEAEs) will be summarized by treatment arm. Treatment-emergent deaths, serious TEAEs, TEAEs with grade 3 or 4 per CTCAE criteria, and TEAEs leading to study or treatment discontinuation will be summarized separately. Surgical complications will be summarized by treatment arm.

Clinically significant changes from baseline in vital signs, laboratory tests, and ECGs will be identified.

Human anti-human antibody data will be summarized in a separate report.

9.3.7. Sensitivity Analyses

Sensitivity analyses will be performed to assess overall survival (OS) by center or groups of centers which are considered to have similar surgical practices. Overall survival (OS) analysis will also be conducted per protocol population.

If there is a large discrepancy between the two arms in the number of patients who undergo surgery, additional analyses to investigate the reasons for the discrepancy will be performed.

A sub-group analysis will be performed to evaluate the differences in efficacy and safety between treatment arms in each subgroup.

9.4. Interim Analysis

An interim analysis is planned to evaluate EFS as a surrogate endpoint for accelerated approval and will be completed when approximately 161 EFS events have occurred. Statistical significance occurs when the estimated hazard ratio is 0.667. When 161 EFS events are available at approximately 24 months into the trial, enrollment will be complete (i.e., 280 patients).

At the time of this EFS analysis, an interim look of OS will be performed by the DMC for lack of benefit analysis, using an O'Brien-Fleming monitoring boundary as a reference..

After the interim analysis, to protect the integrity of the OS data for the final analysis, confidentiality of the emerging OS data will be maintained. (Fleming 2018)Details surrounding the planned Interim Analysis will be described in the Interim Analysis Plan (IAP).

9.5. Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will include detailed analysis methods, statistical models, definitions, as well as data handling rules. The SAP will be finalized prior to database lock.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Data Quality Assurance

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by FibroGen and its designee(s), as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, ICH E6 (GCP), and other applicable regulations.

This study will be monitored by FibroGen or designee in accordance with GCP, and may be audited or reviewed by an independent Quality Assurance department, IRB/IEC, and/or regulatory authorities. This implies that monitors and auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the study and will have direct access to data/source documents, including the subject's file. By participating in this study, Investigators agree to this requirement.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents.
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IRT, clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

Measures will be undertaken to protect the confidentiality of records that could identify subjects, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

10.2. Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, and/or an IRB/IEC may visit the investigator site to perform audits or inspections, including source data verification and source documentation review. The Investigator will allow the sponsor auditor (or designee), regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts (e.g. medical records) and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements.

The investigator must contact the sponsor, or its third party representative (CRO), immediately if notified by a regulatory authority of an inspection pertaining to this study.

11. ETHICS

11.1. Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirements, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

11.2. Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or as required by the policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required reports submitted to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen or designee. A copy of the signed FDA Form 1572 or other qualified investigator statement (as required) must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen or its designee. Written documentation of IRB/IEC approval must be received before the amendment is implemented.

Investigators must maintain a list of appropriate qualified persons to whom the investigator has delegated significant trial-related duties and update the list as staff and their delegated responsibilities change.

11.3. Subject Information and Consent

Prior to participation in any study-specific procedures, the subject must sign (note: all references to "subject" in this section refers to the study subject or his/her legally acceptable representative) an IRB/IEC-approved written Informed Consent Form in his/her native language. The approved written informed consent must adhere to all applicable laws in regards to the safety and confidentiality of the subjects. To obtain and document informed consent, the Investigator should comply with applicable regulations, and adhere to ICH GCP standards and the ethical principles in the Declaration of Helsinki (October 2008).

The language in the written information about the study should be as non-technical as practical and should be understandable to the subject. Before informed consent is obtained, the Investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written Informed Consent Form should be signed and personally dated by the subject and the person

who conducted the informed consent discussion, with any additional signatures obtained as required by applicable local regulations and IRB/IEC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All subjects will receive a copy of the signed and dated Informed Consent Form.

If there are any changes to the IRB/IEC approved ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF, if/as required by the IRB/IEC.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

11.4. Subject Confidentiality

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

The processing of personal data in pursuit of this study will be limited to those data that are reasonably necessary to investigate the utility of the study medications used in this study. These data will be processed with adequate precautions to ensure confidentiality according to local laws.

FibroGen ensures that the personal data are:

- collected for a specified and legitimate purpose
- processed fairly and lawfully
- accurate and up to date

Explicit consent for the processing of personal data will be obtained prospectively from the participating subject. FibroGen and/or designees whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. This confidentiality will be maintained throughout the complete data processing.

Study subjects will be entitled to request confirmation of the existence of personal data held by FibroGen and will have the right to rectify erroneous or inaccurate data prior to database lock.

12. DATA HANDLING AND RECORD KEEPING

12.1. Source Documents

Source documents are original documents, data, and records necessary for the reconstruction and evaluation of the clinical study. The investigator or designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs and resolved queries.

12.2. Direct Access to Source Documents

The investigator must provide direct access to source data and source documents for trial-related monitoring, audits, IRB/IEC review, and regulatory authority inspection. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information and medical records.

12.3. Data Collection, Handling, and Verification

All required data will either be entered onto CRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data (i.e. CRFs and queries) throughout the duration of the study and prior to study completion, ensuring that all data are verifiable with source documents.

12.4. Protocol Deviations

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol violation or deviation to the IRB/IEC, FibroGen, and to the regulatory authorities, if required.

During the COVID-19 global pandemic, sites may have deviated from the protocol due to local/site restrictions that were beyond their control. A study specific memo was issued to all sites providing guidance for conducting this clinical trial during COVID. Protocol deviations related to COVID will be captured in the final protocol deviation listing.

12.5. Retention of Data

A FibroGen representative will inform the Investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or FibroGen or designee, the Investigator agrees to keep records, including the identity of all participating subjects (eg, subject identification code list and all source documents), all original signed ICFs, copies of all CRFs, original laboratory reports, detailed records of drug disposition and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, the Investigator may need to retain these documents for a longer period if required by the applicable regulatory requirements or by an agreement with FibroGen.

12.6. Financial Disclosure

The Investigator's disclosable financial interests must be obtained prior to initiation of the study site, at completion of the study at the investigational site, and 1 year following study completion.

The Investigator should promptly update this information if any relevant changes occur during the above described period.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff to the form FDA 1572 must complete the Investigator Financial Disclosure Form at the beginning of his/her participation in the study. The Investigator Financial Disclosure Form for any Investigator(s) leaving the clinical site prior to study completion will be obtained prior to study completion.

13. PUBLICATION POLICY

The data and results of the study will be owned solely by FibroGen and shall be confidential information of FibroGen, subject to the Investigator's publication rights, described below and if any outlined in the Clinical Trial Agreement. It is understood by the Investigator that FibroGen may use the information developed in this clinical study in connection with the development of its compounds and therefore, may disclose it as required to other clinical investigators, the Licensing Authority or to regulatory agencies of other governments. To allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide and disclose test results and all data developed during this study to FibroGen.

Any publication or presentation of the results of this clinical study by the Investigator may only be made in strict compliance with the provisions of the Clinical Trial Agreement. Any publication relating to the study shall be made in collaboration with FibroGen. The Investigator should understand that it is not FibroGen’s intention to prevent publication of the data generated in the clinical study. However, FibroGen reserves the right to control the form and timing of such publication for commercial reasons. The Study Center and Investigator shall adhere to the publication language as outlined in both the Clinical Trial Agreement and the protocol. To the extent there is any conflict or ambiguity between Clinical Trial Agreement and the protocol, the publication terms in the Clinical Trial Agreement shall prevail.

14. REFERENCES

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APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessments[a]	Screening Period[b]	Cycle 1			Cycles 2-6			End of Treatment[c]	Safety Follow-up Visit	Final Safety Follow-up Contact	Surgical Resection[d]	Surgical Follow-up[e]	Follow-up[f]
	30 days	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	~2 weeks post-last dose	~28 days post-last dose	~60 days post-last dose	4-8 weeks post-last dose	90 days post discharge	Up to 6 years
Written Informed Consent	X												
Inclusion/Exclusion Criteria[b]	X												
Demographics/Medical History[g]	X												
Vital Signs/Weight[h] (include height at screening)	X	X	X	X	X	X	X	X	X				
Disease Stage (TNM)	X							X					
Performance status[i]	X	X			X			X	X				
Physical Exam[j]	X	X	X	X	X		X	X	X				
12-Lead EKG[k]	X	X			X			X					
CBC/Chemistry	X	X	X	X	X	X	X	X	X				
Specialty Labs (PK/PD)		See Appendix 2 for details.											
Pregnancy Test[l]	X	X			X			X					
Chemotherapy Regimen (G/NP or FOLFIRINOX)		See section 6.1.2 or 6.1.3 for details			See section 6.1.2 or 6.1.3 for details								
FG-3019 or placebo[m]		X	X[m]	X	X		X						
CA19-9[n]		X			X			X	X			X	
PET	X							X[o]					
CT[p]	X	Q8W until PD is detected						X[p]					X[p]
EORTC-QLQ-C30[q]		X			X			X	X				
PRO-CTCAE Questionnaire[q]		X	X	X	X	X[q]	X	X	X				
AEs/CMs[r]	X	X	X	X	X	X	X	X	X	X[r]			X[r]

Eligibility for Surgical Exploration[s]									X				
Surgery/Outcomes[t]											X		
Surgical Complications												X	
Progression/Survival/ Follow-on Treatment													X

CBC = complete blood count; CT = computer tomography; ECOG = Eastern Cooperative Oncology Group; EKG = electrocardiogram; EOT = end of treatment; FDG PET = [^{18}F]-fluorodeoxyglucose-positron emission tomography.

a. All visits (including the EOT visit) should occur within ±2 days of protocol specified time point during the neoadjuvant treatment period. The Safety Follow-up and the Surgical Follow-up visit should occur within ±3 days of the specified time point. Visit windows should be calculated based on the previous study visit date, NOT Cycle 1 Day 1.

b. All screening activities should be conducted within 30 days prior to Day 1 Cycle 1. A diagnostic biopsy, which may be performed per SOC, is required for histological or cytological confirmation of PDAC.

c. Subjects who complete 6 cycles of study treatment or discontinue early will undergo an End of Treatment visit approximately 2 weeks following their last dose. All final efficacy assessments will be performed. Subjects who complete 6 cycles of treatment will be evaluated by the central review team to determine eligibility for surgical exploration.

d. All surgeries will occur within 4-8 weeks from the subjects' last dose. Surgery will be performed in accordance with institutional standards and SOPs. Surgeons performing surgery for this study will be trained on the protocol. Tumor tissue will be collected during surgical resection and provided to central pathology for determination of surgical outcome.

e. All subjects who undergo surgical exploration will be followed for surgical safety for 90 days (± 3 days) post discharge, in accordance with the institutions' standard of care. A clinic visit should be scheduled to review surgical complications (if any) and collect CA19-9.

f. All subjects will be followed in Long Term Follow-up for progression, survival and any additional anti-cancer therapy (follow-on treatment for pancreatic cancer) until the last subject to complete treatment has been followed for 18 months post-last dose. It is recommended that Long Term Follow-up be conducted approximately every 3 months.

g. Medical history includes smoking history.

h. Height is collected during screening only.

i. ECOG to be evaluated at baseline, Day 1 of each treatment Cycle, and EOT. Karnofsky scores will be evaluated at EOT only.

j. A full physical exam is required during screening and on Day 1 of each treatment cycle.

k. A 12-lead EKG will be performed during screening, on Day 1 of each cycle and EOT.

l. A serum pregnancy test is required for all females of childbearing potential during screening. The central lab will provide results for the screening serum pregnancy test. Additionally, any female of childbearing potential must have a negative serum or urine pregnancy test confirmed at the site on Day 1 of each cycle (prior to study drug administration) and at EOT.

m. Dosing for pamrevlumab (or placebo) will be based on the weight obtained on Day 1 of each dosing cycle (i.e., Cycle 1 Day 1, Cycle 2 Day 1. An additional dose of pamrevlumab or placebo to be administered on Day 8 of Cycle 1 only. Pamrevlumab (or placebo) to be infused over 1 hour (± 15 minutes) following infusion of chemotherapy agents.

o. If a subject discontinues treatment early, an EOT PET scan is required unless the baseline PET was performed less than 8 weeks from EOT.

p. A baseline CT scan will be conducted during the screening period and approximately every 8 weeks thereafter until disease progression is detected by central imaging review:

- For subjects who complete 6 cycles of treatment, the EOT scan will be evaluated by the central review board in determination of surgical eligibility.
- If a subject completes 6 cycles of treatment without evidence of disease progression, but does not undergo surgical exploration, CT scans should continue to be collected approximately every 8 weeks and submitted for central review until progression is detected (per RECIST 1.1).
- If a subject undergoes surgical exploration and resection, CT scans should be conducted approximately every 4 months following for up to 2 years post-resection and approximately every 6 months from 2-5 years post-resection.
- If recurrence of disease is suspected clinically at any time during the post-resection follow-up, a CT scan may be performed "off schedule" and submitted to central imaging for review/confirmation of progression/recurrence.

q. All PROs to be collected prior to dosing where applicable. PRO-CTCAE™ questionnaire will be administered on Days 1, 8 and 15 of Cycles 1-3 and Day 1 and 15 of each treatment cycle thereafter and at the EOT and Safety follow-up visits.

r. Adverse events and concomitant medications are collected from Day 1 of the study through 60 days following a subject's last dose of study treatment. Serious adverse events should be collected/reported from the signing of Informed Consent through 60 days following the subject's last dose of study treatment. A Safety Follow-up visit must be conducted ~28 days post-last dose and a final safety follow-up contact (via phone) must be conducted ~60 days post-last dose. Additionally, pamrevlumab related SAEs (including deaths) that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

s. Eligibility for surgical exploration per protocol will be determined by a central review board. However, ultimately, the decision to operate on a subject lies with the site PI/surgeon. See Section 7.1.4 for details.

t. Tumor tissue will only be collected during resection. Surgical outcomes of R0, R1 and R2 will be determined by central pathological review of tissue samples collected per the study specific pathology protocol during surgical resection. Tissue collected during resection may also be evaluated for exploratory analysis (i.e. review of slides or digital images for purposes other than determining resection outcome).

APPENDIX 2. PHARMACOKINETIC AND PHARMACODYNAMIC SAMPLING TIMES

TIME POINT[a]			Pamrevlumab (Plasma)	HAHA (Plasma)	HAHA-NA[d] (Plasma)	CTGF (Plasma)	Biomarker (Plasma)	Tumor Tissue
STUDY PERIOD	**DAY**	**TIME**						
Cycle 1	1	Pre-dose [b]	X	X		X	X	
		Post-dose [c]	X					
	8	Pre-dose [b]	X	X				
		Post-dose [c]	X					
	15	Pre-dose [b]	X	X				
		Post-dose [c]	X					
Cycle 6	1	Pre-dose [b]	X	X				
		Post-dose [c]	X					
	28/EOT		X	X			X	
Safety FU Visit	28 days post last dose			X	X	X		
Surgery	4-8 weeks post last dose							X

CTGF = connective tissue growth factor; EOT = end of treatment; HAHA = human anti-human antibody

a. For all time points, the actual time of sample collection will be captured.

b. Pre-dose is within 2 hours prior to the start of the pamrevlumab/placebo infusion. Recommendation to collect just prior to the start of the chemotherapy infusions.

c. Post-dose is during 30 minutes to 2 hours post-end pamrevlumab or placebo infusion.

d. HAHA-NA samples will be collected from all subjects at the Safety Follow-up visit. Samples/subjects with positive/specific HAHA results will be subject to evaluation of neutralizing antibody assays and analyses.

APPENDIX 3. PERFORMANCE STATUS SCALES

Performance Status Criteria			
ECOG (Zubrod)		**Karnofsky**	
Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; eg, light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or do active work.
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.

ECOG = Eastern Cooperative Oncology Group

Cancer Therapy Evaluation Program
Common Toxicity Criteria, Version 2.0
DCTD, NCI, NIH, DHHS March 1998

Revised March 23, 1998
Publish Date: April 30, 1999

APPENDIX 4. CLAVIEN-DINDO CLASSIFICATION OF SURGICAL COMPLICATIONS

Grades	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. This grade also includes blood transfusion and total parenteral nutrition.
III	Requiring surgical, endoscopic or radiological intervention. A: intervention not under general anaesthesia B: intervention under general anaesthesia
IV	Life-threatening complication (including central nerve system complications) requiring IC/ICU-management. A: single organ dysfunction (including dialysis) B: multi organ dysfunction
V	Death of patient
Reference: Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13.	

APPENDIX 5: NCCN GUIDELINES VERSION 2.2018

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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Discussion

CRITERIA DEFINING RESECTABILITY STATUS[a]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some panel members prefer these criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[b]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° Body and tail: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

[a]Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014 Jan; 270(1):248-260.
[b]Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PANC-B

Signature Page for VV-CLIN-012753 v1.0

Approval Task	[redacted] 17-May-2022 00:59:48 GMT+0000

Signature Page for VV-CLIN-012753 v1.0