DISCLOSURE

REDACTED PROTOCOL

ABI-007-PANC-007

NAB-PACLITAXEL (ABRAXANE®) PLUS GEMCITABINE IN SUBJECTS WITH LOCALLY ADVANCED PANCREATIC CANCER (LAPC): AN INTERNATIONAL, OPEN-LABEL, MULTI-CENTER, PHASE 2 STUDY (LAPACT)

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PROTOCOL SUMMARY

Study Title

nab®[1]-paclitaxel (Abraxane®) plus gemcitabine in subjects with locally advanced pancreatic cancer (LAPC): An international, open-label, multi-center, Phase 2 study (LAPACT).

Indication

Locally advanced pancreatic cancer.

Objectives

Primary

- To evaluate the time to treatment failure (TTF) in LAPC subjects treated with *nab*-paclitaxel plus gemcitabine as induction therapy followed by Investigator's Choice of treatment

Secondary

- To evaluate the disease control rate (DCR) after the first 6 cycles of *nab*-paclitaxel plus gemcitabine
- To evaluate the overall response rate (ORR)
- To evaluate the overall progression-free survival (PFS) and overall survival (OS)
- To assess the overall safety profile
- To evaluate the subject's health-related quality of life (QoL)

CCI [redacted]

Study Design

This is an international, non-randomized, open-label, multi-center, Phase 2 study in subjects with LAPC treated with *nab*-paclitaxel plus gemcitabine for 6 cycles followed by an Investigator's Choice of continuation of treatment with *nab*-paclitaxel plus gemcitabine, chemoradiation therapy, or surgery.

Approximately 110 subjects with LAPC will be enrolled in the study. Subjects will be followed until documented progression of disease, withdrawal of consent, lost to follow-up, or death.

Study Population

Subjects with LAPC with no prior anticancer therapy for pancreatic cancer and ≥ 18 years old will be eligible for this study.

[1] *nab*® is a registered trademark of Celgene Corporation.

Length of Study

Enrollment in the study is expected to take approximately 24 months. The total length of this study with treatment and follow-up for OS is estimated to last approximately 3.5 years or until up to 95% of survival data have been collected, whichever comes first.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary [CCI] analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan (SAP), whichever is the later date.

Study Treatments

nab-Paclitaxel plus Gemcitabine for 6 Cycles

Approximately 110 subjects eligible for treatment with *nab*-paclitaxel plus gemcitabine for 6 cycles will be enrolled, provided all inclusion/exclusion criteria are met within a 14-day screening period prior to Cycle 1 Day 1.

Treatment will commence on Day 1 for each of 6 cycles:

- *nab*-Paclitaxel 125 mg/m^2 intravenous (IV) infusion over approximately 30 to 45 minutes on Days 1, 8, and 15, followed by gemcitabine 1000 mg/m^2 IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle

Up to 2 dose reductions to 100 mg/m^2 and 75 mg/m^2 for *nab*-paclitaxel and 800 mg/m^2 and 600 mg/m^2 for gemcitabine are allowed (see Section 8.2.1.2).

Once 6 cycles have been completed, subjects without disease progression or unacceptable toxicity will continue on to the Investigator's Choice part of the study (see Investigator's Choice below).

At any time during the study, subjects with disease progression or unacceptable toxicity will be discontinued from the study treatment.

Investigator's Choice

For subjects who complete 6 cycles of *nab*-paclitaxel plus gemcitabine without disease progression or unacceptable toxicities, the investigator will determine which of the following options are best for the subject:

- Continuation of *nab*-paclitaxel plus gemcitabine therapy

  OR

- Chemoradiation therapy consisting of the concurrent use of capecitabine or gemcitabine with radiation according to institutional practice

  OR

- Surgical intervention

If the Investigator's Choice is to continue treatment with *nab*-paclitaxel plus gemcitabine, treatment should continue on schedule as per prior cycles of therapy until disease progression or unacceptable toxicity.

If the Investigator's Choice is chemoradiation therapy, a minimum of 3 weeks must have elapsed between the last chemotherapy infusion and the initiation of chemoradiotherapy.

If tumor response allows a surgical intervention, the subject will be eligible for that treatment as deemed appropriate by the investigator. Surgical intervention may occur prior to completing the planned 6 cycles of *nab*-paclitaxel plus gemcitabine if subjects demonstrate a major response to therapy. In case of surgery, the delay may vary depending upon the surgery planning; however, the chemotherapy-induced neutropenia nadir should be avoided.

Statistical Summary

This is an international, non-randomized, open-label, multi-center, Phase 2 study which is designed in order to examine and better understand the place for *nab*-paclitaxel plus gemcitabine within the current treatment paradigms in LAPC. The use of data from this Phase 2 study will be utilized in planning the study design for the Phase 3 program.

An interim analysis of DCR will be conducted approximately after all subjects have completed 6 cycles of *nab*-paclitaxel plus gemcitabine, discontinued therapy due to disease progression, died (death by any cause), or started on a new non-protocol-defined anticancer therapy prior to completing 6 cycles of therapy.

Statistical analyses for the primary and key secondary endpoints of the study are described below. Additional detail on the analyses of these endpoints will be described in the SAP.

The SAP supersedes the analyses described in the protocol should there be differences between the two. Further details related to the statistical analyses and sample size determination can be found in Section 10 of this protocol.

Overview of Efficacy Assessments

Time-to-treatment failure is the primary endpoint for this study and is defined as the time after the first dose of study therapy to discontinuation of study therapy due to disease progression, death (by any cause), or the start of a non-protocol-defined anticancer therapy. If a subject does not progress, die, or start a non-protocol-defined anticancer therapy, or if a subject discontinued study therapy, then the subject will be censored as of the last tumor assessment date. Although the sample size for the study was estimated to detect a 30% increase in the median TTF observed in the randomized international Phase 3 study in the metastatic population (MPACT, CA046, NCT00394251), no formal statistical testing will be done with this endpoint. The TTF will be summarized using standard Kaplan-Meier methods. Median TTF and 2-sided 90% confidence interval (CI) will be reported with the accompanying Kaplan-Meier curve.

The secondary efficacy endpoints are DCR at 6 months, ORR, PFS and OS. Details pertaining to the analyses of these endpoints are presented in Section 10.6.2 of this protocol.

Overview of Safety Assessments

All subjects who receive at least 1 dose of *nab*-paclitaxel plus gemcitabine will be evaluated for safety. The number and percent of subjects reporting adverse events (AEs, including treatment-emergent laboratory abnormalities) will be summarized by system organ class and preferred term. All serious adverse events (SAEs) will be tabulated separately as well as included with all reported AEs.

Sample Size

The sample size estimation of 100 subjects provides a sufficient sample in the Intent-to-treat (ITT) population having 80% power to detect a 30% increase in the median TTF of 5.1 to 6.6 months. The null (H_o) and alternative (H_a) hypotheses for this endpoint is as follows, where ***M*** is the median TTF and 5.1 is the median TTF observed in the CA046 study:

H_o: $\boldsymbol{M \leq 5.1}$

H_a: $\boldsymbol{M > 5.1}$

The sample size is calculated assuming a one-sided alpha of 0.05, that subjects will be enrolling for 24 months and that each subject will be followed for a minimum of 1 year. One hundred ten subjects will be enrolled assuming a 10% drop out rate.

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1. INTRODUCTION

1.1. Pancreatic Cancer

Worldwide, pancreatic cancer is the thirteenth most common cancer, with 278,684 new cases diagnosed in 2008. The prognosis is poor, and as a result, pancreatic cancer is the eighth leading cause of cancer-related death worldwide, with an estimated 266,669 deaths in 2008 (CancerStats, 2011). Pancreatic cancer is the fourth leading cause of cancer-related death in the United States (US), with an estimated 39,590 deaths from the disease and an estimated 46,420 new cases expected in 2014 (Siegel, 2014). The incidence of pancreatic cancer is higher in men than women and increases with age, with 90% of pancreatic cancer presenting in subjects over the age of 55 years and more than 70% presenting over the age of 65 years (Howlader, 2013). In Europe, pancreatic cancer is the fourth leading cause of cancer-related death with 80,266 deaths predicted in 2013 (Malvezzi, 2013). Forecasts from the United Nations, World Population Prospects, GLOBOCAN 2012 data for cancer incidence and mortality predicted that the incidence of new cases of pancreatic cancer in the European Union (EU) to be 83,262 cases by 2015 (Ferlay, 2010). As in the US, the pancreatic cancer incidence in the EU is higher in men than women (Seufferlein, 2012), and incidence also increases with age.

The pancreas is composed of 2 main cell types: exocrine (cells that produce digestive enzymes) and endocrine (cells of the islets of Langerhans, that produce among others the hormones insulin and glucagon). Exocrine tumors are by far the most common type of pancreatic cancer, with adenocarcinoma accounting for about 95% of cancers of the exocrine pancreas (ACS, 2013). The focus of the proposed study is pancreatic adenocarcinoma.

The prognosis of subjects with adenocarcinoma is very poor with an overall median survival of 5 to 8 months and fewer than 5% of long-term survival for more than 5 years (Werner, 2013).

Surgical resection of the pancreatic cancer and subsequent adjuvant chemotherapy is the main treatment option required to achieve long-term survival. It can be achieved in about 15% to 20% of subjects (Werner, 2013). For the vast majority of the subjects, the treatment will be palliative in nature consisting of chemotherapy alone or best supportive care for metastatic patients and chemotherapy with or without radiation for locally advanced disease.

1.2. Locally Advanced Pancreatic Cancer

Locally advanced pancreatic cancer (LAPC) is typically too advanced to be removed surgically but still has no distant metastasis. The tumor of the pancreas head or body grow near the mesenteric vessels and the celiac trunk. It is defined anatomically by superior mesenteric artery encasement, aortic invasion, portal vein occlusion, and superior mesenteric vein involvement if not amenable to reconstruction.

At diagnosis, 30% to 35% of patients with pancreatic cancer have a locally advanced unresectable disease. There is currently no consensus on the accepted standard of care for the treatment of LAPC, although chemotherapy alone is considered the preferred treatment option by some oncologists, and chemotherapy followed by chemoradiation or upfront chemoradiation the preferred option by other oncologists. Historically, small randomized trials using chemotherapy and older radiation techniques did not result in better systemic control of the disease and were unable to establish role of chemoradiation (Philip, 2011).

The last generation of clinical trials using gemcitabine as the backbone of chemotherapy or radiation showed a median survival between 11 and 16 months in patients with LAPC (Hammel, 2013; Loehrer, 2011; Philip, 2011). Two new regimens, FOLFIRINOX and *nab*-paclitaxel/gemcitabine, demonstrated a superior efficacy compared to gemcitabine alone in metastatic pancreatic adenocarcinoma (Conroy, 2011; Von Hoff, 2013). In the same period of time, radiation techniques have considerably improved, and biomarkers are being tested to better identify the right populations to be treated. The coming generation of clinical trials are using new effective regimens and techniques in selected patients, and are expected to improve the efficacy of the treatment for LAPC.

1.3. *nab*-Paclitaxel (Abraxane)

nab-Paclitaxel is a proprietary solvent-free, protein-stabilized formulation of paclitaxel comprised of paclitaxel and human albumin in a noncrystalline amorphous state, with a mean particle size of approximately 130 nanometers. *nab*-Paclitaxel was designed to improve the chemotherapeutic effects of paclitaxel by exploiting endogenous transport pathways to deliver higher doses of paclitaxel to the tumor and to reduce the solvent-related hypersensitivity and other toxicities associated with Taxol® (paclitaxel) injections, the solvent Cremophor EL, and ethanol vehicle. *nab*-Paclitaxel provides unique tumor selective localization through enhanced transport across endothelial cell monolayers, increased drug accumulation in tumors (potentially through macropinocytosis (Commisso, 2013), and overall improved pharmacokinetics compared with solvent-based paclitaxel. Furthermore, *nab*-paclitaxel synergizes with gemcitabine in preclinical models. The Cremophor EL-free medium enables *nab*-paclitaxel to be given at a higher dose and in a shorter duration without the need for premedication to prevent solvent-related hypersensitivity reactions (Desai, 2006).

As of August 2014, *nab*-paclitaxel is approved under the trade name of Abraxane in over 50 countries/regions, including the US, Canada, India, EU/European Economic Area (EEA), South Korea, China, Australia, United Arab Emirates, Nepal, New Zealand, Japan, Russia, Sri Lanka, Argentina, Hong Kong, Lebanon, Ecuador, India, Singapore and Chile, for the treatment of patients with metastatic breast cancer. Abraxane is also approved for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in the US, Japan, Argentina, Australia, New Zealand, Ecuador and Chile for the treatment of advanced gastric cancer in Japan, and for the first-line treatment of metastatic adenocarcinoma of the pancreas in the US, EU/EEA, Australia, New Zealand, Argentina, Lebanon, Ecuador and Canada. *nab*-Paclitaxel alone and in combination is being evaluated as a chemotherapeutic agent for the treatment of patients with various solid tumor malignancies.

Please refer to the Investigator's Brochure for more detail on and concerning the available preclinical, pharmacology, toxicology, drug metabolism, clinical study data, and AE profile of *nab*-paclitaxel.

1.3.1. Preclinical and Clinical Experience with *nab*-Paclitaxel Plus Gemcitabine in Pancreatic Cancer

Preclinical studies have demonstrated that *nab*-paclitaxel may play a role in sensitizing the tumor to chemotherapeutic agents and specifically increases the antitumor efficacy when combined with gemcitabine. While the mechanism of action for the synergy is unclear, preclinical studies

have generated hypothetical models. One hypothesis is a remodeling and weakening of the stroma barrier, allowing the chemotherapeutic agents to have better access to the tumor cells. Weakening the tumor-stroma barrier is particularly important in cancer that is characterized by dense stroma, such as pancreatic cancer. In mice with primary patient-derived pancreatic tumor xenografts, *nab*-paclitaxel plus gemcitabine versus gemcitabine alone resulted in increased tumor regression and depleted the desmoplastic stroma as demonstrated by the disorganized collagen type 1 fibers of reduced density after 4 weeks of treatment (Von Hoff, 2011). In this study, the intratumoral concentration of gemcitabine was increased by 2.8-fold after 5 days of treatment when *nab*-paclitaxel was added to gemcitabine. It was hypothesized that *nab*-paclitaxel plays a role in reducing the dense stroma to facilitate increased intratumoral gemcitabine uptake. In additional preclinical studies in genetically engineered mouse models of pancreatic adenocarcinoma, the coadministration of *nab*-paclitaxel and gemcitabine also demonstrated tumor regression and increased intratumoral gemcitabine levels after 8 days of treatment. Apoptosis of tumor epithelial cells were observed; however, there were no changes in stromal components or collagen density in this treatment model (Frese, 2012). The increased intratumoral gemcitabine levels were attributed to a marked decrease in the primary gemcitabine metabolizing enzyme, cytidine deaminase. Finally, a recent clinical study in subjects with resectable pancreatic cancer treated with neoadjuvant *nab*-paclitaxel plus gemcitabine showed reduction in fibrotic collagenous stroma, further supporting a stroma active mechanism for *nab*-paclitaxel (Alvarez, 2013).

In a clinical Phase 1/2 dose-ranging study (CA040, NCT003980860), *nab*-paclitaxel plus gemcitabine antitumor activity and tolerability were established in patients who had no prior treatment for metastatic pancreatic cancer (Von Hoff, 2011). The maximum tolerated dose and recommended dose for further studies was determined to be 125 mg/m^2 *nab*-paclitaxel in combination with 1000 mg/m^2 gemcitabine.

In the subsequent randomized international Phase 3 study (MPACT, CA046, NCT00394251) that enrolled 861 patients with metastatic pancreatic cancer, *nab*-paclitaxel in combination with gemcitabine exhibited a clinically meaningful, statistically significant improvement in overall survival (OS) and progression-free survival (PFS). The median OS (primary endpoint) in the ITT population was 8.5 months (95% CI = 7.89-9.53) with *nab*-paclitaxel/gemcitabine compared with 6.7 months (95% CI = 6.01-7.23) with gemcitabine, $p < 0.0001$, hazard ratio (HR) = 0.72 (95% CI = 0.617-0.835). Long-term survival was improved in the *nab*-paclitaxel/gemcitabine arm versus gemcitabine alone, with a 59% increase at 1 year (35% versus 22%) and doubling at 2 years (9% versus 4%). The secondary (PFS, overall response rate [ORR]) and most of all other efficacy endpoints showed consistent, statistically significant improvements with *nab*-paclitaxel plus gemcitabine, supporting the results from the primary analysis of OS. Specifically, PFS (by independent review) was 5.5 months (95% CI = 4.47-5.95) versus 3.7 months (95% CI = 3.61-4.04) in the *nab*-paclitaxel/gemcitabine arm versus gemcitabine alone arms, respectively $p < 0.0001$; HR = 0.69; 95% CI = 0.581-0.821). The improvement in PFS corresponded to a 31% reduction in the risk of progression or death with *nab*-paclitaxel plus gemcitabine. The estimated median time to treatment failure (TTF) was 5.1 months in the *nab*-paclitaxel plus gemcitabine arm and 3.6 months in the gemcitabine arm (HR = 0.70; 95% CI = 0.604-0.803). Furthermore, in this study of metastatic unresectable adenocarcinoma of the pancreas, subjects in the combination arm were on therapy longer than those receiving single agent gemcitabine, indicating disease improvement and tolerable treatment (Von Hoff, 2013). The suitability of the

dosing regimen was confirmed by the observation that the majority of patients did not require a dose reduction, and that 71% of *nab*-paclitaxel doses were delivered at the starting dose of 125 mg/m^2. The safety profile for both regimens was consistent with previous reports. Serious life-threatening toxicities were not increased; adverse events (AEs) were acceptable and manageable. The most notable differences in toxicity between the 2 treatment arms was peripheral neuropathy, which was cumulative and rapidly reversible with dose delay and reduction, and neutropenia, which was also manageable with dose delays and dose reductions. The incremental risks of sepsis and pneumonitis were managed by protocol amendments to increase awareness, and for early diagnosis and treatment to reduce the risk of fatal outcomes.

As a result of the clinically meaningful benefit observed in the MPACT trial, the 2013 National Comprehensive Cancer Network (NCCN) guidelines were updated to include *nab*-paclitaxel plus gemcitabine as a Category 1 treatment option for patients with metastatic pancreatic adenocarcinoma (NCCN, 2013), and the 2014 NCCN guidelines recommend *nab*-paclitaxel plus gemcitabine in patients with LAPC "based on extrapolation from randomized trials in patients in metastatic disease" (NCCN, 2014).

1.4. Study Rationale

Single agent gemcitabine has been the standard of chemotherapy of pancreatic adenocarcinoma since its approval with a median survival of approximately 6 months and a response rate below 10% (Burris, 1997). In metastatic disease, *nab*-paclitaxel in combination with gemcitabine has demonstrated improved median survival of 8.5 month compared with 6.7 months with gemcitabine alone (HR = 0.72, CI = 0.617-0.835) and a response rate of 23% by independent review and 29% by investigator assessment. The estimated median TTF was 5.1 months in the *nab*-paclitaxel plus gemcitabine arm and 3.6 months in the gemcitabine arm (HR = 0.70; 95% CI = 0.604-0.803) (Study CA046). This positive outcome is very encouraging and needs to be further explored in the locally advanced setting where the chance of improving the patient's clinical benefit are higher, and there remains an unmet medical need. More effective chemotherapy during a sufficient period of time may increase the systemic effect of *nab*-paclitaxel and its benefit in this patient population.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To evaluate the TTF in LAPC subjects treated with *nab*-paclitaxel plus gemcitabine as induction therapy followed by Investigator's Choice of treatment

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the disease control rate (DCR) after the first 6 cycles of *nab*-paclitaxel plus gemcitabine
- To evaluate the ORR
- To evaluate the overall PFS and OS
- To assess the overall safety profile
- To evaluate the subject's health-related QoL

CCI [redacted]

3. STUDY ENDPOINTS

All primary, secondary [redacted] analyses will be based on the ITT population unless otherwise specified. Safety analyses will be performed on the Treated population, which consists of all subjects who take at least 1 dose of IP (referring to both *nab*-paclitaxel and gemcitabine).

All applicable efficacy endpoints will be evaluated by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1 (Eisenhauer, 2009).

3.1. Primary Endpoint

The primary endpoint is TTF, measured as the time after the first dose of study therapy to treatment failure. Treatment failure is defined as discontinuation of study therapy due to disease progression, death (by any cause), or the start of a non-protocol-defined anticancer therapy.

3.2. Secondary Endpoints

3.2.1. Efficacy Endpoints

The secondary efficacy endpoints are:

- The DCR after 6 cycles of *nab*-paclitaxel plus gemcitabine, defined as the combined incidence of complete response (CR), partial response (PR) and stable disease (SD) measured at the End of Treatment visit
- The ORR, defined as the combined incidence of CR and PR
- The PFS defined as the time after the first dose of study therapy to disease progression or death (by any cause)
- The OS defined as the time after the first dose of study therapy to death (by any cause)
- Differences in outcomes from baseline, during treatment, and after treatment with *nab*-paclitaxel plus gemcitabine for the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ), EORTC QLQ-C30 and QLQ-PAN26

3.2.2. Safety Endpoints

- The incidence of treatment-emergent AEs, serious AEs (SAEs), laboratory abnormalities and other safety parameters

[redacted]

4. OVERALL STUDY DESIGN

4.1. Study Design

This is an international, non-randomized, open-label, multi-center, Phase 2 study in subjects with LAPC treated with *nab*-paclitaxel plus gemcitabine for 6 cycles followed by an Investigator's Choice of continuation of treatment with *nab*-paclitaxel plus gemcitabine, chemoradiation therapy, or surgery.

Subjects will be considered active study participants from enrollment up to, but not including, survival follow-up period.

4.1.1. *nab*-Paclitaxel plus Gemcitabine for 6 Cycles

Approximately 110 subjects eligible for treatment with *nab*-paclitaxel plus gemcitabine for 6 cycles will be enrolled, provided all inclusion/exclusion criteria are met within a 14-day screening period prior to Cycle 1 Day 1.

Treatment will commence on Day 1 for 6 cycles:

- *nab*-Paclitaxel 125 mg/m^2 intravenous (IV) infusion over approximately 30 to 45 minutes on Days 1, 8, and 15, followed by gemcitabine 1000 mg/m^2 IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle

Once 6 cycles have been completed, subjects without disease progression or unacceptable toxicity will continue on to the Investigator's Choice part of the study (Section 4.1.2).

At any time during the study, subjects with disease progression or unacceptable toxicity will be discontinued from the study treatment.

4.1.2. Investigator's Choice

For those subjects who complete 6 cycles of *nab*-paclitaxel and gemcitabine without disease progression or unacceptable toxicities, the Investigator will then determine which of the following options are best for the subject:

- Continuation of *nab*-paclitaxel and gemcitabine therapy

  OR

- Chemoradiation therapy consisting of the concurrent use of capecitabine or gemcitabine with radiation according to institutional practice

  OR

- Surgical intervention

If the Investigator's Choice is to continue treatment with *nab*-paclitaxel plus gemcitabine, treatment should continue on schedule as per prior cycles of therapy until disease progression or unacceptable toxicity.

If the Investigator's Choice is chemoradiation therapy, a minimum of 3 weeks must have elapsed between the last chemotherapy infusion and the initiation of the chemoradiotherapy.

If tumor response allows a surgical intervention, the subject will be eligible for that treatment as deemed appropriate by the investigator. Surgical intervention may occur prior to completing the planned 6 cycles of *nab*-paclitaxel plus gemcitabine if subjects demonstrate a major response to therapy. In case of surgery, the delay may vary depending upon the surgery planning; however, the chemotherapy-induced neutropenia nadir should be avoided.

No additional non-protocol-defined anticancer agents are allowed during study treatment.

Protocol defined anticancer agents are:

- *nab*-paclitaxel plus gemcitabine used during the induction phase, or
- Investigator's Choice of continuing chemotherapy with:
  - *nab*-paclitaxel plus gemcitabine
  - chemoradiation consisting of the concurrent use of capecitabine or gemcitabine with radiation according to institutional standard, or
  - surgery

All supportive care (including but not limited to growth factors, antiemetics, analgesics) is permitted as per the Investigator's discretion and should be administered according to local institutional practice.

During the study, subjects will have computed tomography (CT) or magnetic resonance imaging (MRI) scans every 56 days (-3/+7 days) until documented progression of disease, withdrawal of consent from active participation in the study, lost to follow-up, or death. Tumor evaluations will be assessed by the investigative sites and response will be determined according to RECIST v1.1 guidelines.

All scheduled laboratory samples will be performed locally. Local laboratory values that are considered abnormal and clinically significant will be recorded as an AE or SAE and also recorded on the laboratory electronic case report form (eCRF).

Safety data will be reviewed on an ongoing basis throughout the study by the study Medical Monitor and drug safety physician.

4.1.3. Follow-up Period

Safety Follow-up

Subjects who discontinue treatment with *nab*-paclitaxel plus gemcitabine for any reason will have a safety follow-up visit 28 days after treatment discontinuation.

Subjects who are planned to undergo chemoradiation or surgery will have safety visit pre-treatment (with chemoradiation or surgery), at 28 days after discontinuation with chemoradiation, or 28 days post surgery.

Efficacy Follow-up

Subjects who discontinue treatment without disease progression will continue to have CT/MRI scans every 56 days (-3/+7 days) until documented disease progression, withdrawal of consent, lost to follow-up, or death (by any cause), whichever is earliest.

Additionally, subjects will be followed for OS and post-study anticancer therapies approximately every 90 days by phone or review of medical records until death, withdrawal of consent, or lost to follow-up.

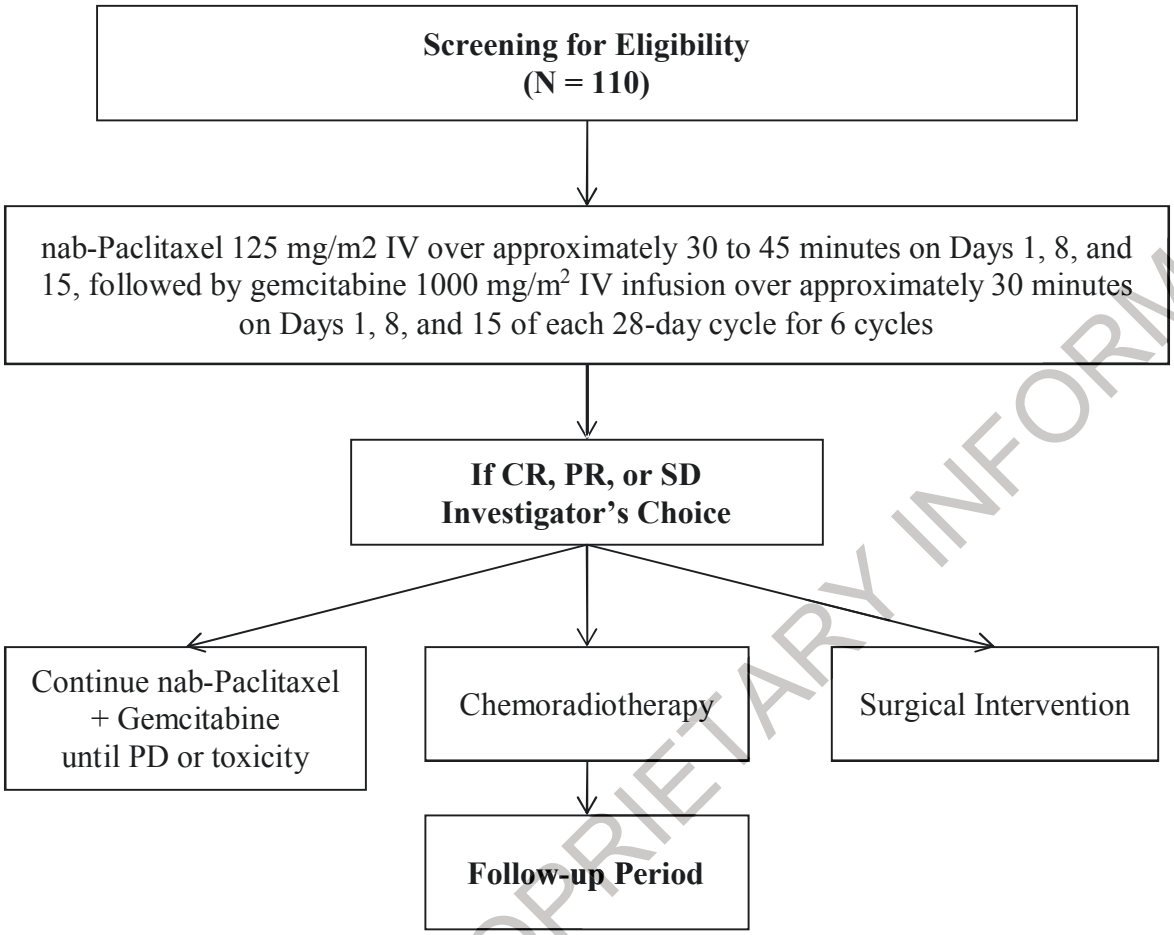
4.2. Study Design Rationale

Despite the development of new systemic therapies for metastatic pancreatic cancer, there is no established combination chemotherapy regimen for LAPC.

The study design of this trial (Figure 1) is meant to reproduce the current predominant clinical practice with chemotherapy being prescribed upfront, followed by the options of chemoradiation therapy or, in rare cases, surgery. The combination of *nab*-paclitaxel plus gemcitabine as the upfront chemotherapy is expected to bring a more effective systemic control of the disease and may become the therapy backbone for the treatment of LAPC and testing of targeted agents in the future. In addition, with better systemic therapies, the role of chemoradiation therapy may be better studied. The purpose of this study, however, is not to prospectively test the role of chemoradiotherapy in LAPC.

The promising activity with *nab*-paclitaxel plus gemcitabine in metastatic pancreatic cancer underscore the hypothesis for this study in subjects with LAPC. The *nab*-paclitaxel plus gemcitabine regimen used for this study will be in accordance with Food and Drug Administration (FDA) and European Commission (EC) approved label for metastatic pancreatic cancer: *nab*-paclitaxel 125 mg/m^2 IV infusion over 30 minutes on Days 1, 8, and 15, followed by gemcitabine 1000 mg/m^2 IV infusion over 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Figure 1: Overall Study Design



CR = complete response; IV = intravenously; PD = progressive disease; PR = partial response; SD = stable disease.

4.3. Study Duration

The enrollment period will last approximately 24 months. The total length of this study with enrollment into the *nab*-paclitaxel plus gemcitabine for 6 cycles, Investigator's Choice, and follow-up is estimated to be approximately 3.5 years or until up to 95% of survival data have been collected, whichever comes first.

4.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary CCI analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

5. TABLE OF EVENTS

Table 1: Table of Events – Induction: *nab*-Paclitaxel Plus Gemcitabine

Assessment	Reference to Protocol Section	Screening/ Baseline	Treatment Period Every 28-day Cycle				Follow-Up Period[a]	
		Day -14 to Day -1	Day 1 (±2 days)	Day 8 (±1 days)	Day 15 (±1 days)	Every 56 days (-3/+7 days) (starting C1D1)	28-day Follow-up Visit (after last dose of IP)	Survival Follow-Up Every 90 Days (± 14 Days)
Informed Consent	Section 6	X	-	-	-	-	-	-
Medical History, Prior Medication and Procedures of Special Interest	Sections 6.1, 6.5	X	-	-	-	-	-	-
Demographics	Section 6.2	X	-	-	-	-	-	-
nab-Paclitaxel Administration/Accountability	Section 4.1.1	-	X	X	X	-	-	-
Gemcitabine Administration/Accountability	Section 4.1.1	-	X	X	X	-	-	-
Physical Examination	Section 6.3	Will be done as per standard of care during the study and as clinically indicated						
Vital Signs	Section 6.4							
Pregnancy Test (Serum)	Section 6.6	X	-	-	-	-	-	-
Pregnancy Test (Urine)	Section 6.6						X	
CT Scan and Any Other Studies Required for Tumor Imaging	Section 6.7	X	-	-	-	X	X	-
Height	Section 6.8	X	-	-	-	-	-	-
Weight	Section 6.8	X	X	-	-	-	-	-
ECOG Performance Status	Section 6.9	X	X	-	-	-	X	-

Table 1: Table of Events – Induction: *nab*-Paclitaxel Plus Gemcitabine (Continued)

Assessment	Reference to Protocol Section	Screening/ Baseline	Treatment Period Every 28-day Cycle				Follow-Up Period	
		Day -14 to Day -1	Day 1 (±2 days)	Day 8 (±1 days)	Day 15 (±1 days)	Every 56 days (-3/+7 days) (starting C1D1)	28-day Follow-up Visit (after last dose of IP)	Survival Follow-Up Every 90 Days (± 14 Days)
Concomitant Medications/Procedures of Special Interest	Section 6.10	X	X	-	-	-	X	-
Peripheral Neuropathy Assessment	Section 6.11	X	X	-	-	-	X	-
Adverse Event Evaluation	Section 6.12	After signing ICF and until 28 days after the last dose of IP or at the 28-day Follow-up Visit, whichever occurs later. Not during survival unless it is a suspected SAE (See Section 11.5)						
EORTC QLQ-C30 and QLQ-PAN26	Section 6.13	X	X	-	-	-	X	-
Complete and Differential Blood Count	Section 6.14	X	X	X	X	-	X	-
Serum Chemistry	Section 6.14	X	X	-	-	-	X	-
Serum CA19-9	Section 6.14	X	-	-	-	X	X	-
CCI [redacted]								
Survival Status	Section 6.16	-	-	-	-	-	-	X

AE = adverse event; β-hCG = beta human chorionic gonadotropin; C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC - European Organization for Research and Treatment of Cancer; FCBP = females of childbearing potential; ICF = informed consent form; IP = investigational product; IV = intravenous; MRI = magnetic resonance imaging; QLQ = quality of life questionnaire; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; US = United States.

[a] Refer to Table 2, Table 3 or Table 4 if continuing to Investigator's Choice.

Table 2: Table of Events – Investigator's Choice: Continuing with *nab*-Paclitaxel Plus Gemcitabine

Assessment	Reference to Protocol Section	Treatment Period Every 28-day Cycle				Follow-Up Period	
		Day 1 (±2 days)	Day 8 (±1 days)	Day 15 (±1 days)	Every 56 Days (-3/+7 Days) (Starting C1D1)	28-day Follow-up Visit (after last dose of IP)	Survival Follow-Up Every 90 Days (± 14 Days)
nab-Paclitaxel Administration/Accountability	Section 4.1.1	X	X	X	-	-	-
Gemcitabine Administration/Accountability	Section 4.1.1	X	X	X	-	-	-
Physical Examination	Section 6.3	Will be done as per standard of care during the study and as clinically indicated					
Vital Signs	Section 6.4						
Pregnancy Test (Urine)	Section 6.6	-	-	-	-	X	-
CT Scan and Any Other Studies Required for Tumor Imaging	Section 6.7	X	-	-	X	X	-
Weight	Section 6.8	X	-	-	-	-	-
ECOG Performance Status	Section 6.9	X	-	-	-	X	-
Concomitant Medications/Procedures of Special Interest	Section 6.10	X	-	-	-	X	-
Peripheral Neuropathy Assessment	Section 6.11	X	-	-	-	X	-
Adverse Event Evaluation	Section 6.12	After signing ICF and until 28 days after the last dose of IP or 28-day Follow-up Visit, whichever occurs later. Not during survival unless it is a suspected SAE (See Section 11.5)					
EORTC QLQ-C30 and QLQ-PAN26	Section 6.13	X	-	-	-	X	-
Complete and Differential Blood Count	Section 6.14	X	X	X	-	X	-
Serum Chemistry	Section 6.14	X	-	-	-	X	-
Serum CA19-9	Section 6.14	X	-	-	X	X	-
CCI [redacted]							
Survival Status	Section 6.16	-	-	-	-	-	X

AE = adverse event; β-hCG = beta human chorionic gonadotropin; C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC - European Organization for Research and Treatment of Cancer; ICF = informed consent form; IP = investigational product; IV = intravenous; MRI = magnetic resonance imaging; QLQ = quality of life questionnaire; SAE = serious adverse event; US = United States.

Table 3: Table of Events – Investigator's Choice: Chemoradiation as per Institutional Standard of Care

Assessment	Reference to Protocol Section	Prior to Chemoradiation	Treatment Period (Chemoradiation)		Follow-Up Period	
		28-day Follow-up Visit After Last Dose of IP	Weekly During Chemo-radiation	Every 56 Days (-3/+7 Days) (From C1D1)	28-day Follow-up Visit	Survival Follow-Up Every 90 Days (± 14 Days)
Chemoradiation as per Institutional Standard of Care	Section 4.1.2	-	X	-	-	-
Physical Examination	Section 6.3	Will be done as per standard of care during the study and as clinically indicated				
Vital Signs	Section 6.4					
Pregnancy Test (Urine)	Section 6.6	X	-	-	-	-
CT Scan and any other studies required for tumor imaging	Section 6.7	X	-	X	X	-
ECOG Performance Status	Section 6.9	X	-	-	-	-
Concomitant Medications/Procedures of Special Interest	Section 6.10	X	X	-	-	X
Peripheral Neuropathy Assessment	Section 6.11	X	-	-	-	-
Adverse Events Evaluations	Section 6.12	After signing ICF and until 28 days after the last dose of chemoradiation or the 28-day Follow-up Visit, whichever is later. Not during survival unless it is a suspected SAE (See Section 11.5)				
EORTC QLQ-C30 and QLQ-PAN26	Section 6.13	X	-	-	-	-
Complete and Differential Blood Count	Section 6.14	X	X	-	X	-
Serum Chemistry	Section 6.14	X	X	-	X	-
Serum CA19-9	Section 6.14	X	-	X	X	-
CCI						
Survival Status	Section 6.16	-	-	-	-	X

C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; ICF = informed consent form; IP = investigational product; QLQ = quality of life questionnaire; RECIST = Response Evaluation Criteria in Solid Tumors; US = United States.

Table 4: Table of Events – Investigator's Choice: Surgery as per Institutional Standard of Care

Assessment	Reference to Protocol Section	Prior to Surgery	Treatment Period (Surgery)		Follow-Up Period	
		28-day Follow-up Visit After Last Dose of IP	Day of Surgery	Every 56 Days (-3/+7 Days) (Starting C1D1)	28-day Follow-up Period	Survival Follow-Up Every 90 Days (± 14 Days)
Surgery as per Institutional Standard of Care	Section 4.1.2	-	X	-	-	-
Physical Examination	Section 6.3	Will be done as per standard of care during the study and as clinically indicated				
Vital Signs	Section 6.4					
Pregnancy Test (Urine)	Section 6.6	X	-	-	-	-
CT Scan and any other studies required for tumor imaging	Section 6.7	X	-	X	X	-
ECOG Performance Status	Section 6.9	X	-	-	-	-
Concomitant Medications/Procedures of Special Interest	Section 6.10	X	X	-	X	X
Peripheral Neuropathy Assessment	Section 6.11	X	-	-	-	-
Adverse Events Assessment	Section 6.12	After signing ICF and until 28-days post surgery or the 28-day surgery Follow-up Visit, whichever is later. Not during survival unless it is a suspected SAE (See Section 11.5)				
EORTC QLQ-C30 and QLQ-PAN26	Section 6.13	X	-	-	-	-
Complete and Differential Blood Count	Section 6.14	X	-	-	X	-
Serum Chemistry	Section 6.14	X	-	-	X	-
Serum CA-19-9	Section 6.14	X	-	X	X	-
CCI						
FFPE Tumor Tissue From Surgical Resection	Section 6.15	-	X	-	-	-
Survival Status	Section 6.16	-	-	-	-	X

C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed, paraffin-embedded; ICF = informed consent form; IP = investigational product; QLQ = quality of life questionnaire.

6. PROCEDURES

Subjects will be provided with a written informed consent form (ICF), given the opportunity to ask any questions concerning the study, and will sign an ICF prior to participating in any study procedures. After giving written informed consent, subjects will undergo a screening period to be assessed for eligibility. All subjects who sign an ICF must be screened into the Interactive Randomization Technology (IRT) immediately upon signature on the document. Subjects who do not meet the inclusion/exclusion criteria will be considered screening failures and will not be eligible for the study. Subjects that have satisfied all eligibility criteria after the screening period will be eligible for enrollment. Subjects who screen fail may re-screen up to 3 times and an ICF will need to be signed at each re-screen, as well as repeating screening procedures (some procedures may not need to be repeated if previously completed within 14 days prior to Screening).

Investigators will be asked at subject enrollment what their preferred treatment would be at the conclusion of the 6 cycles of therapy. The intended treatment will then be compared to the actual treatment given at the conclusion of the 6 cycles of therapy.

6.1. Medical History

An abbreviated medical history for pancreatic cancer will be collected. All pancreatic cancer-related medical history should be recorded regardless of time.

6.2. Demographics

Gender, race and other categorical variables will be captured if allowed by local regulations.

6.3. Physical Examinations

Physical examinations will be done as per standard of care during the study and as clinically indicated; however, results will not be collected in the eCRFs (if results are abnormal and clinically significant at Screening, they will be recorded as medical history, and if results are abnormal and clinically significant after Screening, they will be recorded as an AE or SAE).

6.4. Vital Signs

Vital signs (temperature, systolic and diastolic blood pressure and pulse) will be done as per standard of care during the study and as clinically indicated; however, results will not be collected in the eCRFs (if results are abnormal and clinically significant at Screening, they will be recorded as medical history, and if results are abnormal and clinically significant after Screening, they will be recorded as an AE or SAE).

6.5. Prior Medications/Procedures of Special Interest

Prior medications and procedures of special interest (Section 19.2) within 14 days of time of signature on the ICF should be recorded. All pancreatic cancer-related prior medications/procedures should be recorded regardless of time.

6.6. Pregnancy Testing

A serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained in females of childbearing potential (FCBP) at Screening. A serum pregnancy test must be done within 72 hours prior to Cycle 1 Day 1 of starting study therapy. The subject may not receive treatment until the Investigator has verified that the result of the pregnancy test is negative.

A urine pregnancy test must be performed at the 28-day Follow-up Visit after the subject's last dose of IP. See inclusion criteria for pregnancy testing requirements. Any pregnancies that occur in women who have received investigational product (IP) during the study or within 28 days after the last dose of IP, or in the partner of the male subject during the study or within 6 months after the last dose of IP must be immediately reported to Celgene Drug Safety.

6.7. Computed Tomography or Magnetic Resonance Imaging Scan

During the induction period, a CT/MRI scan with and without contrast of the chest, abdomen and pelvis and any other studies required for tumor imaging will be done at Screening, every 56 days (-3/+7 days) (schedule for scans will be based on calendar, not start of cycle), and at the 28-day Follow-up Visit (after the last dose of IP).

During the Investigator's Choice part of the study, scans will be done every 56 days (-3/+7 days) (schedule for scans will be based on calendar, not start of cycle) and at the 28-day Follow-up Visit (after the last dose of IP and chemoradiation), and post surgery (28 days post surgery).

All subjects should have CT/MRI until disease progression, withdrawal of consent from active participation in the study, lost to follow-up, death (by any cause), or the start of a non-protocol-defined anticancer therapy, whichever is the earliest.

Additional CTs may be done at any time during the study if clinically indicated. A baseline MRI scan with contrast may replace a CT scan for tumor assessment based on the decision of the treating oncologist (eg, intolerance to IV contrast dye for CT). In those situations, follow-up scans for tumor assessment must be by MRI.

Screening CT or MRI scans will be de-identified and collected for potential central analysis of eligibility.

6.8. Weight and Height

Weight will be obtained at Screening and at every Day 1 of every cycle during the Treatment Period before the administration of IP. Additional weight measurements may be collected per local standards at any time during the study as needed. Height will only be collected at Screening. All weight and height data will be recorded on eCRFs.

6.9. Eastern Cooperative Oncology Group (ECOG) Performance Score

The ECOG performance score (Section 19.1) will be collected at Screening, Day 1 of every cycle, and at the 28-day Follow-up Visit (after last dose of IP). Additional ECOG performance scores may be collected at any time during the study as needed.

6.10. Concomitant Medications/Procedures of Special Interest

All subjects will have concomitant medications and procedures of special interest (Section 19.2) recorded at the beginning of each cycle from the time of signature on the ICF until the 28-day Follow-up Visit. All pancreatic cancer-related concomitant medications will also be collected during the Survival Follow-Up. For SAEs, all concomitant medications will be collected (Section 9.1).

6.11. Peripheral Neuropathy Assessment

Peripheral neuropathy assessment will be assessed from the time of signature on the ICF and Day 1 of each cycle until the 28-day Follow-up Visit. The occurrence of peripheral neuropathy will be reported by the Investigator per protocol as an AE or SAE. Additional peripheral neuropathy assessments may be done at any time during the study as needed. Subjects with Grade 4 peripheral neuropathy will be discontinued from study treatment.

6.12. Adverse Event Reporting

All subjects will have AEs recorded at each visit from time of signature on the ICF until 28 days after the last dose of IP, or at the 28-day Follow-up Visit, including any unscheduled visits, whichever occurs later.

For subjects who undergo chemoradiation, AEs will be assessed until 28 days after the last dose of chemoradiation or the 28-day chemoradiation Follow-up Visit, whichever is later.

For subjects who undergo surgery, AEs will be assessed until 28 days post surgery or the 28-day surgery Follow-up Visit, whichever is later.

6.13. Quality of Life Questionnaires

The EORTC QLQ-C30 and QLQ-PAN26 questionnaires will be completed at Screening, Day 1 of every cycle and at the 28-day Follow-up Visit during the *nab*-paclitaxel plus gemcitabine induction phase and for subjects continuing *nab*-paclitaxel plus gemcitabine as an Investigator's Choice. Subjects who discontinue the *nab*-paclitaxel plus gemcitabine regimen before completing the treatment cycles should have 1 final quality of life (QoL) data collection at their 28-day Follow-up Visit after the treatment discontinuation and no further QoL data collection is needed. The QoL data generated from these questionnaires will be analyzed per the description in the SAP.

6.14. Laboratory Assessments

All scheduled laboratory samples will be analyzed locally. Laboratory values of special interest (Section 19.3) and laboratory values that are considered abnormal and clinically significant will be recorded as an AE/SAE and also recorded on the laboratory eCRF.

Laboratory assessments to include:

- Clinical chemistry panel (including but not limited to sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), alkaline phosphatase, aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine

aminotransferase/ serum glutamic-pyruvic transaminase (ALT/SGPT), serum albumin, total bilirubin and creatinine) will be collected:

  - at Screening, Day 1 of each dosing cycle of *nab*-paclitaxel plus gemcitabine, and at the 28-day Follow-up Visit
  - weekly during treatment and at follow-up if continuing on chemoradiation
  - 28 days post surgery

- Complete blood count (CBC), differential and platelet count will be collected:
  - at Screening, Day 1, 8, and 15 of each dosing cycle of *nab*-paclitaxel plus gemcitabine, and at the 28-day Follow-up Visit
  - weekly during treatment and at follow-up if continuing on chemoradiation
  - 28 days post surgery
- Serum carbohydrate antigen 19-9 (CA19-9) levels will be collected at the time of every CT/MRI scan assessment

CCI [redacted]

6.16. Survival

Survival follow-up will be by phone or review of medical records approximately every 90 days until withdrawal of consent, lost to follow-up, or death (by any cause). Post-study anticancer therapies as well as their efficacy and tolerability will be recorded in the eCRF for further analysis.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Subjects with LAPC who are ≥ 18 years old will be eligible for this study. Approximately 110 subjects will be enrolled. The study will be conducted in US, Canada, and the EU.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. ≥ 18 years of age at the time of signing the ICF.
2. Histologically or cytologically confirmed adenocarcinoma of the pancreas.
3. Unresectable pancreatic cancer according to radiographic criteria (CT or MRI scans) or exploration:
    a. Superior mesenteric vein and portal vein: occlusion, thrombosis, or encasement extending several centimeters
    b. Superior mesenteric artery: tumor abutment > 180 degrees or thrombosis of artery
    c. Celiac axis: abutment or encasement of the celiac axis
    d. Lymph nodes: involvement
4. Without distant metastasis as defined by CT or MRI scan of the chest, abdomen and pelvis.
5. ECOG performance status of 0 or 1.
6. Acceptable hematology parameters:
    a. Absolute neutrophil count (ANC) ≥ 1500 cell/mm^3
    b. Platelet count ≥ 100,000/mm^3
    c. Hemoglobin (Hgb) ≥ 9 g/dL
7. Acceptable blood chemistry levels:
    a. AST/ SGOT and ALT/ SGPT ≤ 2.5 x upper limit of normal range (ULN)
    b. Total bilirubin ≤ 1.5 ULN
    c. Alkaline phosphatase ≤ 2.5 x ULN
    d. Serum albumin > 3 g/dL
    e. Serum creatinine ≤ 1.5 ULN
8. Female of childbearing potential (FCBP) (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally

postmenopausal for at least 24 consecutive months [ie, has had menses at any time during the preceding 24 consecutive months]) must:

a. Either commit to true abstinence* or agree to the use of 2 physician-approved contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on IP; and for 3 months following the last dose of IP; and

b. Has a negative serum pregnancy test (β-hCG) result at screening

9. Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for 6 months following IP discontinuation, even if he has undergone a successful vasectomy.
10. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures are conducted.
11. Able to adhere to the study visit schedule and other protocol requirements.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Pancreatic tumors of endocrine or mixed origin.
2. Prior anticancer therapy for pancreatic carcinoma.
3. Presence of or history of metastatic pancreatic adenocarcinoma.
4. Any other malignancy within 5 years prior to enrollment, with the exception of adequately treated in-situ carcinoma of the prostate (Gleason score ≤ 7), cervix, uteri, or nonmelanomatous skin cancer (all treatment of which should have been completed 6 months prior to enrollment).
5. Active bacterial, viral, or fungal infection(s) requiring systemic therapy, defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
6. Known infection with hepatitis B or C, or history of human immunodeficiency virus (HIV) infection, or subject receiving immunosuppressive or myelosuppressive medications that would, in the opinion of the Investigator, increase the risk of serious neutropenic complications.
7. History of allergy or hypersensitivity to *nab*-paclitaxel or gemcitabine or any of their excipients.
8. Peripheral sensory neuropathy Grade > 1.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception).

9. Clinically significant ascites.
10. Plastic biliary stent. Metal biliary stent is allowed.
11. Serious medical risk factors involving any of the major organ systems, or serious psychiatric disorders, which could compromise the subject's safety or the integrity of the study data. These include, but are not limited to:
    a. History of connective tissue disorders (eg, lupus, scleroderma, arteritis nodosa)
    b. History of interstitial lung disease, slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, or multiple allergies
    c. History of the following within 6 months prior to Cycle 1 Day 1: a myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association (NYHA) Class III-IV heart failure, uncontrolled hypertension, clinically significant cardiac dysrhythmia or electrocardiogram (ECG) abnormality, cerebrovascular accident, transient ischemic attack, or seizure disorder
12. Enrollment in any other clinical protocol or investigational study with an interventional agent or assessments that may interfere with study procedures.
13. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
14. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
15. Any condition that confounds the ability to interpret data from the study.
16. Unwillingness or inability to comply with study procedures.
17. Pregnant or breast feeding.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Products

nab-Paclitaxel will be supplied by the sponsor and labeled appropriately as investigational material for this study. Labels will bear Celgene's name and address, the protocol number, EudraCT number (if applicable), product name, dosage form and strength, medication identification/kit number, lot number, expiry date, dosing instructions, storage conditions, quantity of IP contained, and required caution statements and/or regulatory statements as applicable.

Gemcitabine will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines.

Additional information may be included on the label as needed or applicable. Label(s) for IP supplied to sites outside the US will contain information as required per local health authority.

The IP supply will be managed by IRT. All IP must be stored in accordance with the product label in a secure area to prevent unauthorized access.

IP refers to both *nab*-paclitaxel and gemcitabine.

8.1.1. Abraxane (*nab*-Paclitaxel)

nab-Paclitaxel will be supplied by the sponsor, Celgene Corporation, in single-use vials in single-count cartons. Each single-use 50 mL vial will contain paclitaxel (100 mg) and human albumin as a stabilizer.

See local prescribing information for Abraxane for detailed instructions on the reconstitution, storage conditions, and IV administration of *nab*-paclitaxel.

Temperature records for *nab*-paclitaxel must be made available to Celgene or other sponsor-nominated monitoring teams for verification of proper IP storage.

8.1.2. Gemcitabine

Gemcitabine is a nucleoside metabolic inhibitor.

Gemcitabine will be supplied or obtained according to local clinical study agreement and in accordance with local guidelines.

See gemcitabine prescribing information for more details on available formulations, preparation, storage conditions, approved indications, known precautions, warnings, and adverse reactions of gemcitabine (see current Prescribing Information).

8.2. Treatment Administration and Schedule

nab-Paclitaxel plus Gemcitabine for 6 Cycles

Approximately 110 subjects eligible for treatment with *nab*-paclitaxel plus gemcitabine for 6 cycles will be enrolled, provided all inclusion/exclusion criteria are met within a 14-day screening period prior to Cycle 1 Day 1.

Treatment will commence on Day 1 for 6 cycles:

- *nab*-Paclitaxel 125 mg/m^2 IV infusion over approximately 30 to 45 minutes on Days 1, 8, and 15, followed by gemcitabine 1000 mg/m^2 IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle

Once 6 cycles have been completed, subjects without disease progression or unacceptable toxicity will continue on to the Investigator's Choice part of the study.

At any time during the study, subjects with disease progression or unacceptable toxicity will be discontinued from the study treatment.

Investigator's Choice

For subjects who complete 6 cycles of *nab*-paclitaxel and gemcitabine without disease progression or unacceptable toxicities, the Investigator will then determine which of the following options are best for the subject:

- Continuation of *nab*-paclitaxel and gemcitabine therapy to disease progression or unacceptable toxicity

  OR

- Chemoradiation therapy consisting of the concurrent use of capecitabine or gemcitabine with radiation according to institutional practice

  OR

- Surgical intervention

Surgical intervention may occur prior to completing the planned 6 cycles of *nab*-paclitaxel plus gemcitabine if subjects demonstrate a major response to therapy.

All IP will be administered by the clinical site, and administration will be documented in the study source record.

8.2.1. Dose Modifications

8.2.1.1. Rules for Dose Omissions and Modified Schedules

If, for administrative reasons, treatment cannot be administered on the planned visit date, IP may be administered ≤ 2 days from the scheduled date. Study treatments days must be 7 or more days apart for each other.

Day 1 Dose Missed

If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the subject (ie, 1-2-3-Rest, X-1-2-3-Rest, etc).

Day 8 Dose Is Missed

If the dose held or missed was to be given on Day 8 of the next cycle, that next cycle continues per protocol, with 1 dose not given (ie, 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc). Day 8 is administered as per cycle calendar if complete blood counts and chemistries permit.

Day 15 Dose Missed

If the dose held or missed was to be given on Day 15 of the next cycle, that week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the subject is considered to have had a x2Q3W (21-day) cycle (ie, 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc).

The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 21 days (except for peripheral neuropathy; see Table 7).

8.2.1.2. Dose Modification Tables

Doses will be reduced for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0.

Two levels of dose modifications for Abraxane and/or gemcitabine are permitted according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction of either IP, further treatment should be discontinued. Dose escalations are prohibited.

Table 5: Dose Modifications

Dose Level	*nab*-Paclitaxel Dose (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]
Study Dose	125	1000
-1	100	800
-2[b]	75	600

[a] Dose reductions may or may not be concomitant, refer to Table 6. If the dose is withheld due to hematologic toxicity on Day 15, resume at the next lower dose level when the subject has adequate absolute neutrophil and platelet counts to begin Day 1 of the next cycle. Refer to Table 6 for specific recommendations regarding dose modifications for Day 1.

[b] A maximum of 2 dose level reductions are allowed.

Subjects experiencing IP-related toxicities that require a delay in scheduled *nab*-paclitaxel or gemcitabine dosing for ≥ 21 days will be discontinued from further treatment in this study (except for peripheral neuropathy; see Table 7).

In the event dose modifications are required at the start of a cycle or within a cycle due to hematologic toxicities of neutropenia and/or thrombocytopenia, doses of *nab*-paclitaxel and gemcitabine may be adjusted as detailed in Table 6. The WBC growth factor may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in subjects with an ANC < 500 cells/mm^3. Subjects not experiencing resolution of neutropenia within 21 days, despite uninterrupted WBC growth factor treatment, will discontinue study treatment. In addition, WBC growth factors may be administered as supportive therapy to recover ANC adequately such that dosing levels may be maintained. If a dose reduction was required due to neutropenia, a dose re-escalation may be considered with continued growth factor support. If hematologic toxicity is restricted to platelet counts alone, dose modification of only gemcitabine could be considered after discussion with the sponsor.

Table 6: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	*nab*-Paclitaxel Dose	Gemcitabine Dose
Day 1	≥ 1500	AND	≥ 100,000	Treat on time at current dose levels	
	< 1500	OR	< 100,000	Delay doses until recovery	
Day 8	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce 1 dose level	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were given without modification:					
Day 15	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce 1 dose level from Day 8; consider following with WBC growth factors for support[a]	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were reduced:					
Day 15	≥ 1000	AND	≥ 75,000	Treat with same doses as Day 8; consider following with WBC growth factors for support[a]	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce 1 dose level from Day 8; consider following with WBC growth factors for support[a]	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were withheld:					
Day 15	≥ 1000	AND	≥ 75,000	Option A: Maintain dose level from Day 1 and follow with WBC growth factors for support[a] OR Option B: Reduce 1 dose levels from Day 1	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Option A: Reduce 1 dose level from Day 1 and follow with WBC growth factors for support[a] OR Option B: Reduce 2 dose levels from Day 1	
	< 500	OR	< 50,000	Withhold doses	

ANC = absolute neutrophil count; WBC = white blood cell.
[a] The use of WBC growth factors is only applicable if the dose-limiting hematologic toxicity was limited to neutropenia or febrile neutropenia.

Dose modifications for other adverse drug reactions are provided in Table 7.

Table 7: Dose Modifications for Other Adverse Drug Reactions

Adverse Drug Reaction	*nab*-Paclitaxel Dose	Gemcitabine Dose
Febrile Neutropenia[a]: Grade 3 or 4	Withhold doses until fever resolves and ANC is ≥ 1500; resume at next lower dose level[b]	
Peripheral Neuropathy: Grade 3	Withhold dose until improvement to ≤ Grade 1; resume at next lower dose level[b]	Treat with same dose
Peripheral Neuropathy: Grade 4	Discontinued from study treatment	
Cutaneous Toxicity: Grade 2 or 3	Withhold dose until improvement to ≤ Grade 1; resume at next lower dose level[b] Discontinue treatment if AE persists	
For all other nonhematologic toxicities (except nausea, vomiting, alopecia and pulmonary embolism) of ≥ Grade 3	Withhold doses until improvement to ≤ Grade 1; resume at next lower dose level[b]	

ADR = adverse drug reaction; ANC = absolute neutrophil count.
[a] White blood cell growth factor may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in subjects with an ANC of < 500 cells/mm^3
[b] See Table 5 for dose level reductions.

8.2.1.3. Administration of Investigational Product to Subjects with Abnormal Hepatic Function

The IP should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the subject is on study should prompt an evaluation to determine the cause, including the possibility of metastatic disease and hepatotoxicity from concurrent medications, alcohol use, or other factors.

8.2.1.4. Pulmonary Embolism and Deep Vein Thrombosis

To resume IP administration in the event of a pulmonary embolism or deep vein thrombosis, subjects must be started on low molecular weight heparin or similar anticoagulation therapy. Grade 4 events must be resolved to Grade ≤ 3 within 21 days to continue IP.

8.2.1.5. Interstitial Pneumonitis

While participating in this study, subjects should be carefully monitored to prevent or minimize the occurrence of interstitial pneumonitis. Careful prestudy screening with continuous on-study monitoring for signs and symptoms is required. Should a subject develop symptoms of pneumonitis during this study, the timely initiation of appropriate management is required. Recommended guidelines are as follows:

1. Before enrollment, evaluate candidate subjects for familial, environmental, or occupational exposure to opportunistic pathogens, and do not enroll those with a history of slowly progressive dyspnea and unproductive cough, or of conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, or multiple allergies.
2. During study treatment, provide close attention to episodes of transient or repeated dyspnea with unproductive persistent cough or fever. Radiographic evaluation with chest x-rays and CT scans (normal or high resolution) may be indicated to evaluate for infiltrates, ground-glass opacities, or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.
3. Infections should be ruled out with routine immunological/microbiological methods. A transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.
4. Administration of IP should be interrupted upon diagnosis of interstitial pneumonitis and subjects permanently discontinued from further IP treatment. After ruling out an infectious etiology, IV high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Subjects with an added immunological agent may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

8.2.1.6. Prophylaxis Against Sepsis

In the metastatic pancreatic cancer Phase 3 study (CA046), an increase in cases of non-neutropenic sepsis was observed with the combination of *nab*-paclitaxel and gemcitabine. An exploratory analysis suggested that the presence of biliary stents may have increased the risk of sepsis in that population. Investigators were to provide oral broad spectrum antibiotics to subjects who were then to initiate these antibiotics at the first occurrence of fever. Subjects enrolled in this clinical trial may not have the same risk of sepsis as metastatic pancreatic cancer patients. Subjects should be advised that there could be an increased risk of serious infection and they should contact their physician for evaluation when they develop a fever. Fever or similar symptoms should be fully evaluated as an early sign of a serious infection (see Section 9.1).

8.2.1.7. Hypersensitivity Reactions

Hypersensitivity reactions are infrequent with *nab*-paclitaxel. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria, require immediate discontinuation of IP administration and aggressive symptomatic therapy.

Subjects who develop a severe hypersensitivity reaction to *nab*-paclitaxel should not be rechallenged.

8.2.2. Overdose

Overdose, as defined for this protocol, refers to *nab*-paclitaxel or gemcitabine dosing only.

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of *nab*-paclitaxel or gemcitabine to a given subject, regardless of any associated AEs or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol-required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. See Section 11.1 for the reporting of AEs associated with overdose.

8.3. Method of Treatment Assignment

Subjects who enter screening will be assigned the next available subject number. All eligible subjects will be enrolled to receive *nab*-paclitaxel in combination with gemcitabine.

8.4. Packaging and Labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

8.5. Investigational Product Accountability and Disposal

Celgene (or its designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction, including the responsibilities for the site versus Celgene (or designee).

The IP refers to both *nab*-paclitaxel and gemcitabine.

Investigational product vials should be disposed of in accordance with institutional/regional requirements, unless otherwise agreed with Celgene. Disposition should be recorded on the Investigational Drug Accountability Record Form.

The Investigator, or designee, shall record the dispensing of IP to subjects in the IP accountability record. The IP record will be made available to Celgene, or other authorized Celgene-designated monitoring personnel, for the purpose of accounting for the IP supply. Inspections of the IP supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Celgene or its designee and a plan for resolution will be documented.

Investigational product will not be loaned or dispensed by the Investigator to another Investigator or site. Under certain circumstances, and with sponsor permission, cooperative groups may manage IP between locations within their network as clinical study agreement and local guidelines permit.

8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF and source documents. The Investigator or designee is responsible for the accountability for all study-specific IP either administered or in their custody during the course of the study.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

All supportive care is permitted.

Ciprofloxacin (or the alternative broad spectrum antibiotic) must be distributed to subject with instructions to begin treatment if they experience a febrile episode (temperature of 38.5°C/101.3°F). Administration of long-term prophylactic ciprofloxacin (or the alternative antibiotic) to prevent recurrences in subjects already having experienced a first febrile episode will be at the discretion of the treating physician.

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from study treatments or disease recurrence. Supportive care, including but not limited to antiemetic medications, may be administered at the discretion of the Investigator.

WBC growth factors may be administered at the discretion of the Investigator, consistent with institutional guidelines and with the Prescribing Information for such growth factors. WBC growth factors should be used only in patients who have demonstrated prior events of neutropenia; primary prophylaxis with WBC growth factors is not permitted.

Erythropoietin may be administered at the discretion of the Investigator, consistent with institutional guidelines.

For information regarding other drugs that may interact with either *nab*-paclitaxel or gemcitabine and affect their metabolism, pharmacokinetics, or excretion, see the *nab*-paclitaxel and gemcitabine package inserts (refer to Prescribing Information).

All concomitant treatments of special interest, including blood and blood products for the treatment of SAEs (Section 19.2), must be reported on the eCRF.

9.2. Prohibited Concomitant Medications and Procedures

Other antineoplastic agents or investigational drugs other than what is specified in the protocol (as defined in Section 4.1.1 and Section 4.1.2) are prohibited.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

Statistical analyses for the primary and key secondary endpoints of the study are described below. Additional detail on the analyses of these endpoints as well as subgroup analyses will be described in the SAP.

The SAP supersedes the analyses described in the protocol should there be differences between the two.

10.1. Overview

This is an international, non-randomized, open-label, multi-center, Phase 2 study of *nab*-paclitaxel plus gemcitabine in subjects with LAPC. This study includes an Investigator's Choice component in order to examine and better understand the place for *nab*-paclitaxel plus gemcitabine within the current treatment paradigms in LAPC. The use of data from this Phase 2 study will be utilized in planning the study design for the Phase 3 program.

This study consists of 2 parts: a fixed treatment part that consists of a single arm where subjects receive *nab*-paclitaxel plus gemcitabine on Days 1, 8, and 15 of each 28-day cycle for 6 cycles. Once 6 cycles have been completed, subjects without disease progression or unacceptable toxicity will continue on to the Investigator's Choice of continuation of treatment with *nab*-paclitaxel plus gemcitabine, chemoradiation therapy, or surgery. If tumor response allows a surgical intervention, the subject will be eligible for that treatment as deemed appropriate by the investigator. Surgical intervention may occur prior to completing the planned 6 cycles of *nab*-paclitaxel plus gemcitabine if subjects demonstrate a major response to therapy.

A consort diagram will be presented showing the relative proportions of subjects going onto *nab*-paclitaxel plus gemcitabine therapy, chemoradiation therapy, or surgical intervention. A data listing will also be provided.

At any time during the study, subjects with disease progression or unacceptable toxicity will be discontinued from the study treatment. During the study, subjects will have CT/MRI scans every 56 days (-3/+7 days) until documented progression of disease, withdrawal of consent from active participation in the study, lost to follow-up, or death. Tumor evaluations will be assessed by the Investigators and response will be determined according to RECIST v1.1 guidelines. Subjects who discontinue treatment without disease progression will continue to have CT/MRI scans every 56 days (-3/+7 days) until disease progression, withdrawal of consent, lost to follow-up, or death. Subjects will then continue to be followed for OS approximately every 90 days by phone or review of medical records.

10.2. Study Population Definitions

The population for this study will consist of all subjects enrolled in the study who were diagnosed with LAPC. The following study populations will be examined:

- Intent-to-treat (ITT) population: The ITT population is defined as all subjects enrolled in the study who receive at least 1 dose of IP
- Per-protocol (PP) population: The PP population is defined as all subjects enrolled in the study who receive at least 1 dose of IP and fulfill the study enrollment criteria.

The PP population may be used for additional analyses which will be described in the SAP

- Treated population: The Treated population consists of all subjects who receive at least 1 dose of *nab*-paclitaxel plus gemcitabine

The primary efficacy analysis will be performed on the ITT population. The secondary efficacy analyses will be performed on the PP population, and the safety analyses will be performed on the Treated population.

10.3. Sample Size and Power Considerations

The primary endpoint for this study is median TTF. The null (H_o) and alternative (H_a) hypotheses for this endpoint is as follows, where ***M*** is the median TTF and 5.1 months is the median TTF observed in the CA046 study:

H_o: $\boldsymbol{M \leq 5.1}$

H_a: $\boldsymbol{M > 5.1}$

A total sample size of 100 subjects will have 80% power to detect a 30% increase in the median TTF of 5.1 to 6.6 months (Table 8). The sample size is calculated assuming a one-sided alpha of 0.05, that subjects will be enrolling for 24 months and that each subject will be followed for a minimum of 1 year. One hundred ten subjects will be enrolled assuming a 10% drop out rate.

Table 8: Power Calculation for Median Time to Treatment Failure and Sample Size

Percent Increase in Median TTF	Median TTF for the Alternative-Hypothesis (Months)	Accrual Duration (Months)	N	Power
20%	6.1	24	100	0.54
		30	100	0.55
30%	**6.6**	**24**	**100**	**0.80**
		30	**100**	**0.81**
50%	7.7	24	100	0.99
		30	100	0.99

TTF = time to treatment failure.

10.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

Subject characteristics including demographics, disease duration, and relevant medical history at baseline will be summarized for the purpose of characterizing the locally advanced subject population.

Prior medications or procedures of special interest (Section 19.2) taken within 30 days of first drug administration and all concomitant medications for the treatment of SAEs will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Classification. The incidence of prior and concomitant medication usage will be summarized.

Investigator's Choice

Investigators will be asked at subject enrollment what their preferred treatment would be at the conclusion of the 6 cycles of therapy. The intended treatment will then be compared to the actual treatment given at the conclusion of the 6 cycles of therapy. A change in the Investigator's preferred treatment will not be considered a treatment failure.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

Subject disposition including the number of subjects enrolled, treated, and each reason for discontinuation of therapy will be summarized for each part of the study.

10.6. Efficacy Analysis

All primary and secondary efficacy analyses will be conducted on the ITT population.

10.6.1. Primary Efficacy Analysis

Time to treatment failure is the primary endpoint for this study and is defined as the time after the first dose of study therapy to discontinuation of study therapy due to disease progression, death (by any cause), or the start of a new non-protocol-defined anticancer therapy. If a subject does not progress, die or start a new non-protocol-defined anticancer therapy, or if a subject discontinued study therapy, then the subject will be censored on the last tumor assessment date. Although the sample size for the study was estimated to detect a 30% increase in the median TTF observed in the CA046 study, no formal statistical testing will be done with this endpoint. The TTF will be summarized using standard Kaplan-Meier methods. Median TTF and a 2-sided 90% CI will be reported with the accompanying Kaplan-Meier curve.

10.6.2. Secondary Efficacy Analyses

Because of the exploratory nature of this study and the lack of statistical testing, no adjustment for multiplicity of endpoints is required.

10.6.2.1. Disease Control Rate at 6 Months

The secondary efficacy endpoint of DCR is calculated by defining responders as the summation of all subjects with CR + PR + SD. To quality for DCR calculation, SD must last for ≥ 16 weeks. This endpoint will be summarized and presented with the 2-sided 90% CI. All subjects discontinued from study due to disease progression, death (by any cause), or the start of a new non-protocol-defined anticancer therapy will be considered non-responders.

10.6.2.2. Overall Response Rate

Overall response rate will be summarized. Subjects with Investigator-determined CR or PR will be considered responders and the ORR will be presented with 90% CIs around the proportion. All subjects discontinued from study due to disease progression, death (by any cause), or the start of a new non-protocol-defined anticancer therapy will be considered non-responders.

10.6.2.3. Progression-free Survival

Progression-free survival is defined as the time after the first dose of study therapy to the start of disease progression or death (by any cause), whichever occurs first. Subjects who do not have disease progression or have not died will be censored at the last known time that the subject was progression-free. If a subject begins a new anticancer therapy or has palliative radiotherapy or surgery at a lesion site prior to documented progression or death then the subject will be censored at the last assessment where the subject was documented as progression-free prior to intervention. Subjects with 2 or more consecutive missing response prior to a visit with documented progression or death will be censored at the last date that the subject was documented to be progression-free.

Progression-free survival will be summarized using standard Kaplan-Meier methods. Median PFS and the 90% CI will be reported with the accompanying Kaplan-Meier curve.

10.6.2.4. Evaluation of Overall Survival

Overall survival is defined as the time after the first dose of study therapy to the date of death (by any cause). Subjects who are alive will be censored at the last known time that the subject was alive.

Overall survival of *nab*-paclitaxel plus gemcitabine will be summarized by median survival time with 90% CI and the accompanying Kaplan-Meier curve.

10.6.2.5. Evaluation of Health-related Quality of Life

Differences in outcomes from baseline, during treatment, and after treatment for the EORTC QLQs, EORTC QLQ-C30 and QLQ-PAN26 will be will be described in an analysis plan separate from the SAP.

CCI [redacted]

[redacted]

10.7. Safety Analysis

All subjects who receive at least 1 dose of *nab*-paclitaxel plus gemcitabine (ie, Treated population; see Section 10.2) will be evaluated for safety. The number and percent of subjects reporting AEs (including treatment-emergent laboratory abnormalities) will be summarized by system organ class, and preferred term. All SAEs will be tabulated separately as well as included with all reported AEs.

10.8. Interim Analysis

An interim analysis of the DCR will be conducted after all subjects have completed 6 cycles of *nab*-paclitaxel plus gemcitabine, discontinued therapy due to disease progression, died from any cause, or started a new non-protocol-defined anticancer therapy prior to completing 6 cycles of therapy. The results of this analysis will be provided in the final clinical study report following study completion.

10.9. Other Topics

No other topic will be studied.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

For the purposes of this study, PD assessed using the RECIST v1.1 guidelines of LAPC will not require reporting as an AE.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.2.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for *nab*-paclitaxel, or gemcitabine overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of IP and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form or approved equivalent form.

Safety Follow-up

Subjects who discontinue treatment with *nab*-paclitaxel plus gemcitabine for any reason will have a Safety Follow-up Visit 28 days or End of Treatment Visit, whichever occurs later).

Subjects who discontinue treatment with *nab*-paclitaxel plus gemcitabine and are planned to undergo chemoradiation or surgery therapy will have the safety visit before that treatment.

For subjects who undergo chemo radiation, AEs will be assessed until 28 days after the last dose of chemoradiation or the 28-day chemoradiation.

For subjects who undergo surgery, AEs will be assessed until 28 days after the surgery.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

11.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.0) http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Adverse events that are not defined in the NCI CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3. Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means the causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject becomes pregnant while the subject is receiving IP or within 6 months of the last dose of IP, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. The IP may need to be discontinued in the male subject, but may be resumed later at the discretion of the Investigator and medical monitor.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to

Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent to at least 28 days after the last dose of IP) and those made known to the Investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to *nab*-paclitaxel based on the Investigator's Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the EEA, Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on IP for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP, gemcitabine, based on the United Kingdom Summary of Product Characteristics (SmPC).

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

12. DISCONTINUATIONS

The reason for study discontinuation should be recorded in the eCRF and in the source documents. The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor with the decision to discontinued/withdraw a subject due to an AE (any unacceptable toxicity) and forward appropriate supporting documents for review and discussion.

All subjects who are withdrawn from the study should complete all protocol-required evaluations scheduled for early termination at the time of withdrawal. Since follow-up of subjects who discontinue prematurely is of particular importance, every attempt should be made to collect all survival information and LAPC treatment/therapy, unless the subject has specifically withdrawn consent from further follow-up. The Investigator should make every effort to obtain minimal information regarding the subject's survival status before determining the subject is lost to follow-up.

12.1. Study Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the IP:

- Adverse event(s)
- Disease progression
- Investigator's decision
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

All subjects discontinued from *nab*-paclitaxel plus gemcitabine for any reason will have a treatment discontinuation visit at the time of *nab*-paclitaxel plus gemcitabine discontinuation and should undergo early termination procedures.

All subjects discontinued from *nab*-paclitaxel plus gemcitabine will be followed for a period of 28 days after PFS or early discontinuation, or until the date of the last study visit (whichever is longer) for the collection of AEs.

Additionally subjects who withdraw from or complete treatment should not be withdrawn from the study (unless specifically requested) and should be followed up for progressive disease, survival and any new therapy given.

12.2. Study Discontinuation

The following **are** considered sufficient reasons for discontinuing a subject from the study:

- Withdrawal of consent (decision from the subject not to provide follow-up information)

- Investigator's decision
- Death
- Lost to follow-up

The following **may be** considered a sufficient reason for discontinuing a subject from the study:

- Protocol violation
- AE or unacceptable toxicity

12.3. Subject Replacement

Subjects who discontinue will not be replaced.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page).This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/Contract Research Organization (CRO) Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the subject's entry into the study and of the informed consent process should be recorded in the subject's source documents including the date. The original ICF signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the subject. In addition, if a protocol is amended and it impacts the content of the informed consent, the ICF must be revised. Subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the subject and by the person consenting the subject must be maintained in the Investigator's study files and a copy given to the subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Investigational Product can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reason*ab*le medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2. Data Management

Data will be entered into the clinical database per Celgene Standard Operating Procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- Investigational Product accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is u*nab*le to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is u*nab*le to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, IP storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection and order of authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in the study.

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19. APPENDICES

19.1. ECOG Performance Status Score

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

Source: Oken, 1982.

19.2. List of Concomitant Medications or Procedures of Special Interest

- Anti-infectives
- Steroids
- Narcotics
- IV fluids
- For blood support (eg, transfusions, growth factors)
- For cardiac events (eg, myocardial infarction, angina pectoris, heart failure, uncontrolled hypertension, clinically significant cardiac dysrhythmia or electrocardiogram (ECG) abnormality)
- For cerebrovascular accident, transient ischemic attack, or seizure
- For peripheral sensory neuropathy
- For ascites
- For lung disease
- For prevention or therapy of nausea/vomiting

19.3. List of Laboratory Values of Special Interest

- Liver functions
- Renal functions
- Albumin levels

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: PPD
Title: PPD
Date: Thursday, 15 February 2018, 06:09 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Administrative Amendment to update details of Medical Monitor and Therapy Area Head. Updated details found in the MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION and CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE sections.