CANCER

IIT2018-29-HENDIFAR-PNCX3

PANCREATIC-ENZYME REPLACEMENT THERAPY WITH PANCREAZE (PANCRELIPASE) DELAYED-RELEASE IN ADDITION TO STANDARD OF CARE FOR BORDERLINE RESECTABLE, LOCALLY ADVANCED AND ADVANCED PANCREATIC ADENOCARCINOMA PATIENTS (PANCAX-3) WITH CACHEXIA AND EXOCRINE PANCREATIC INSUFFICIENCY

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Funding Source: **Vivus**

NCT Number: **NCT04098237**

Initial version: **Protocol Version 1 dated 12 SEP 2019**

Current version: **Protocol Version 7 dated 18MAY2023**

Prior version: **Protocol Version 6 dated 14OCT2022**
Protocol Version 5 dated 17JAN2022
Protocol Version 4 dated 13 SEP 2021
Protocol Version 3 dated 04 JAN 2021
Protocol Version 2 dated 28 MAY 2020
Protocol Version 2.1 dated 02 SEP 2020

Protocol v7 dated 18MAY2023

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

Signature: _____ **Date:** _____

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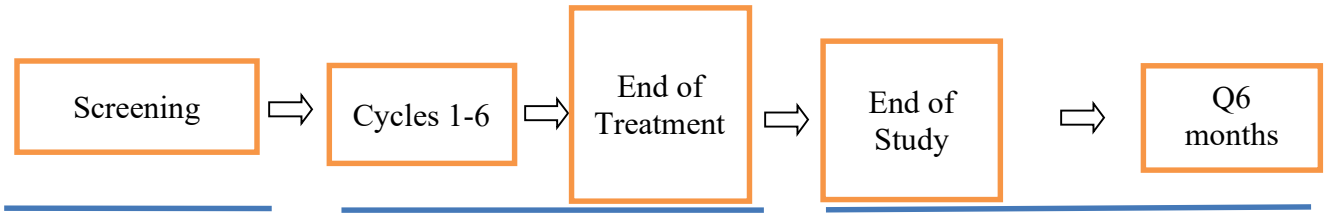
LIST OF ABBREVIATIONS

5FU	5- fluorouracil
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
CA19-9	Carbohydrate antigen 19-9
CACS	Cancer anorexia cachexia syndrome
CBC	Complete Blood Count
CCK	Cholecystokinin
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRP	C Reactive Protein
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EPI	Exocrine Pancreatic Insufficiency
EOT	End-of-Treatment
FA	Folinic Acid (Leucovorin)
GLP-1	Glucagon-like peptide-1
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IL1a	Interleukin 1-alpha
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
LMF	Lipid Mobilizing Factors
LBM	Lean Body Mass
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PAWL	Pancreatic Cancer-Associated Weight Loss
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progression of Disease
PFS	Progression Free Survival
PR	Partial Response
PYY	Peptide YY

STUDY SCHEMA



Screening Phase
1. Informed consent
2. Screening
3. Eligibility review
4. Measure stool fecal elastase
5. Measure fat-soluble vitamins

Treatment Phase
Cycle = 28 days
1. Measure weight stability
2. Assess 24-hour caloric intake
3. Assess stool frequency and consistency
4. Evaluate microbiome
5. Assess activity levels
6. Measure quality of life
7. Assess inflammatory biomarkers
8. Assess the presence of frailty phenotype
9. Assess body composition

End-of-Treatment
After C6D28:
1. Return pill bottles
2. Transition to Soc enzymes

Follow-up Phase
Safety evaluation
Measure fat-soluble vitamins
Survival
Optional sub-study: Follow-up activity tracking

STUDY SUMMARY

Title	Pancreatic-enzyme replacement therapy with pancreaze (pancrelipase) delayed-release in addition to standard of care for borderline resectable, locally advanced and advanced pancreatic adenocarcinoma patients (PANCAX-3) with cachexia and exocrine pancreatic insufficiency.
Short Title	PANCAX-3
Protocol Number	IIT2018-29-Hendifar-PNCX3
Phase	Phase 2
Methodology	Single arm, Single center
Accrual Duration	18 months
Study Duration	Approximately 6 months from screening to end of treatment assessment. Subjects will continue to be followed for survival for 36 months.
Study Center(s)	Single-center, Cedars-Sinai Medical Center
Objectives	1. Feasibility to complete pancreatic enzyme replacement therapy at 8 weeks 2. Measure weight stability at baseline and day 1 of every cycle for 6 months 3. 24-hour caloric intake at baseline, C3D1, and end-of-study 4. Stool frequency at baseline and C3D1 5. Quality of life assessment baseline and day 1 of every other cycle for 6 months 6. Fitness tracking will be assessed with a wrist-worn wearable activity monitor (e.g., Fitbit Charge HR) continuously from day 1 of cycle 1 until the end of study visit.
Number of Subjects	Up to 40 patients (30 evaluable patients)
Diagnosis and Main Inclusion Criteria	1. Age ≥ 18 years of age 2. Biopsy proven pancreatic cancer 3. Borderline resectable, locally advanced or advanced disease 4. Clinical diagnosis of exocrine pancreatic insufficiency 5. Cachexia defined as 5% weight loss in last 6 months
Study Product(s), Dose, Route, Regimen	Subjects meeting enrollment criteria will be given Pancrelipase (84,000 lipase units per main meal and 42,000 lipase units per snack). This will be in addition to standard of care procedures including consult with a dietitian and systemic chemotherapy. Subjects will undergo treatment with pancreatic enzymes indefinitely as per standard therapy for patients with EPI.
Duration of administration	Daily for 24 weeks
Statistical Methodology	A single institution, phase 2 clinical trial.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Pancreatic-enzyme replacement therapy (PERT) is the standard of care to prevent maldigestion, malnutrition, and excessive weight loss in patients with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (CP) or pancreatic surgery (PS). The utility of this therapy for patients with EPI in the setting of pancreatic cancer is unclear.

Pancreatic cancer is the fourth leading cause of cancer related deaths in the United States and associated with poor prognosis. EPI is a common complication of pancreatic cancer. There are several mechanisms for this, which includes tumor induced pancreatic duct obstruction, pancreatic fibrosis and atrophy. Under normal circumstances, digestive enzymes secreted from the pancreas are essential for digestion of proteins and fats. Impairment in enzyme secretion can lead to malabsorption of these compounds producing symptoms of delayed gastric emptying, increased bloating, abdominal fullness/discomfort, nausea, and early satiety in addition to potential nutrient deficiencies. Studies have shown a prevalence varying from 50-89% demonstrated by low fecal elastase [1-3]. Studies have shown that cachexia worsens the prognosis of patients with pancreatic cancer [4, 5]. Weight loss has also been associated with a poorer quality of life in patients with pancreatic cancer and those with stabilization of weight reported a greater global quality of life score[5]. Studies have shown small peak or no peak in the release of pancreatic enzymes in patients with pancreatic cancer[6] . DiMagno showed lower trypsin, lipase and bicarbonate secretion in patients with non-resectable pancreatic cancer and pancreatic duct obstruction [7]

Pancreatic enzyme supplementation has demonstrated benefit for patients with EPI due to chronic pancreatitis. Two previous randomized-controlled trials have evaluated the impact of enzyme supplementation among patients with chronic pancreatitis. Both studies demonstrated improvement in measures of fat absorption (coefficient of fat absorption, fecal fat excretion) among patients treated with enzyme supplements [8, 9]. In addition, the study reported by Safdi et al also noted that the enzyme treatment group experienced reduced stool frequency, improved stool consistency and greater physician-assessed global symptom improvement [10]. No serious adverse events related to study medication occurred in either trial.

However, the evidence for the use of pancreatic enzymes in pancreatic cancer is limited. Despite this, according to the guidelines published in Gut in 2005 for the management of patients with pancreatic cancer, pancreatic enzymes supplementation should be used to maintain weight and increase quality of life [11]. A double blinded randomized controlled trial looking at 21 patients with unresectable cancer in the head of the pancreas with obstructive jaundice and suspected pancreatic duct obstruction were randomized to placebo or enteric coated pancreatin enzyme supplementation. Patients were given 25000 units of lipase with snacks and 50,000 units with meals. The investigators found that patients on the enzyme supplementation gained 1.2% body weight compared to placebo who lost 3.7% body weight over 4-week follow-up. Fat absorption coefficient improved by 12% in those receiving enzymes [12]. Dominguez Munoz et al presented an abstract at the APA in 2013 of a retrospective non-randomized case series of 76 patients with nonresectable pancreatic cancer who were receiving Creon replacement with nutritional counseling and palliative care or standard palliative care without enzyme therapy. They found that the median survival of patients who were receiving pancreatic enzyme therapy was longer than those with standard palliative care (301 days versus 89 days). This study was limited by the lack of measurement of EPI [13].

Our objective is to assess weight stability, functional changes, and quality of life when pancreaze (pancrelipase) delayed-release 84,000-lipase unit capsules, for main meals, and 42,000-lipase unit capsules, for snacks, are added to standard of care in patients with EPI due to pancreatic adenocarcinoma. This will be the first prospective study of this particular formulation in addition to standard of care in advanced pancreatic cancer patients. We will treat 30 consecutive patients with borderline resectable, locally advanced and advanced pancreatic cancer who present with weight loss and exocrine pancreatic insufficiency with this advanced formulation of pancreaze.

Standard of Care Nutrition Screening and Clinical Assessment:

A full nutrition assessment involves the following elements: obtaining a food history, evaluation of anthropometric measurements, review of medical history, biochemical data, medical tests and procedures, and completion of a nutrition-focused physical assessment [14]. Routine assessment of food intake should include patient estimate of overall food intake and 24-h food recall [15]. An oncology focused assessment also involves reviewing the oncologic treatment plan with the goal to determine current and anticipated nutrition issues [16-18]. This information is all assimilated and used to formulate a plan to address existing and potential influences on malnutrition.
Dietitians play a central role in the successful management of pancreatic cancer-associated weight loss (PAWL). Nutrition interventions for PAWL have improved weight [19], quality of life, and outcomes [14, 20, 21]. Dietitians can provide essential dietary suggestions, identify pancreatic exocrine insufficiency, and provide recommendations for oral nutritional supplementation and specialized nutrition support [22]. Dietitians may also provide more detailed advice on diet and pancreatic enzyme supplementation for management of symptoms of EPI [23-26].

1.2 Study Agent(s) Background and Associated Known Toxicities

Pancreaze (pancrelipase) Delayed-Release Capsules is a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, or other conditions.

Pancreatic-enzyme replacement therapy (PERT) is the standard of care to prevent maldigestion, malnutrition, and excessive weight loss in patients with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (CP) or pancreatic surgery (PS). Pancreaze is available in dosages of 2,600, 4,200, 10,500, 16,800, and 21,000-lipase units per capsule.

1.3 Rationale

Pancrelipase has been approved for the use in patients with exocrine pancreatic insufficiency due to cystic fibrosis or other conditions. In randomized studies it has improved fat absorption and decreased the stool frequency in these patients. However, its utility in advanced pancreatic cancer patients has not been evaluated to date.

Advanced pancreatic adenocarcinoma is characterized by progressive weight loss and nutritional deterioration [27]. It is estimated that up to 80% of these patients present with cachexia [28]. This wasting has been linked not only to survival, but also to alterations in host defenses, functional ability, and quality of life [29]. There have been few studies of whether nutritional support improves outcomes for these patients and the results have been inconsistent [30, 31]. This is despite evidence that artificial nutrition can improve performance status and other outcomes in terminal cancer patients [32].

Exocrine pancreatic insufficiency (EPI), which results from tumor-induced damage to the pancreatic parenchyma, obstruction of the pancreatic duct, and surgical removal of pancreatic tissue, is considered a major cause of this syndrome[33]. This deficiency impairs the body's ability to absorb fat, carbohydrates, and proteins, which results in steatorrhea, abdominal cramps, weight loss, and malnutrition[34]. Associated symptoms include foul-smelling flatulence, diarrhea, greasy stools, abdominal discomfort following meals, pain, bloating, and belching[34]. EPI is estimated to

affect 68% to 92% of patients with pancreatic cancer prior to surgery and as many as 94% of those following surgery[35].

There are few effective therapies for pancreatic cancer and none for its associated cachexia. Megesterol and Marinol are routinely prescribed for appetite stimulation but not effective[36]. Therapies attempting diet modifications and supplements have also failed to improve outcomes[37].

One study randomized patients with pancreatic cancer to either 6 capsules of a high-dose pancreatic enzyme supplement per day or placebo for 8 weeks, with both groups receiving dietary counseling. Patients taking PERT gained 1.2% of their body weight compared with a 3.7% weight loss in the placebo group, with a mean difference in percentage of body weight change of 4.9% (P =.02; 95% confidence interval [CI] for the difference, 0.9%-8.9%). In addition, the fat absorption coefficient improved by 12% among those treated with PERT, while declining 8% for patients taking placebo (P =.13)[33].

Patients with borderline resectable, locally advanced, and advanced disease have distinct treatment paradigms and clinical outcomes. It is known that malabsorption is present in 68-92% of patients at diagnosis and most patients have associated symptoms [3, 6, 35, 38, 39]. In patients who had surgical resections, PERT was shown to improve the digestion of fat and associated symptoms of malabsorption [40]. As the cancer advances and the disease has spread to more area within the pancreas, the reliance on PERT is often increasingly recommended as the pancreas becomes less able to perform normal functions to aid in digestion of food. Previous studies have shown that lower trypsin, lipase and bicarbonate secretion are present in patients with non-resectable pancreatic cancer and pancreatic ductal obstruction [7]. As the utility of PERT varies with respect to each of the three cohorts of patients, it will be important to understand if there are some patient cohorts with an increased need for PERT.

1.4 Correlative Studies

In this prospective study, we will evaluate stool frequency and quality associated with the use of pancreatic enzyme replacement therapy. Recent evidence also suggests that gut microbial metabolites regulate the release of the gut hormones, which is associated with changes in gut microflora and its metabolic products [38, 39][38, 39]. In the last few years, several studies have presented substantial data suggesting a role for the oral and gut microbiota in pancreatic cancer [40]. In this context, the generation of germ-free mice has been extremely valuable to better understand the influence of the microbiome in carcinogenesis. In most models, these animals are less inclined to carcinogenesis, probably due to decreased tumor-associated inflammation [41]. The same profile is observed in antibiotic-treated mice that reduces the microbial load of the gut [42] Remarkably, bowel sterilization with broad-spectrum antibiotics appears to be protective in acute pancreatitis as well.

It would be important to better understand the microbiome associated with exocrine pancreatic insufficiency. We would also measure the changes in the microbiome as a response to the enzyme therapy.

We will also further explore the impact of this therapy on quality life, pain and patient reported outcomes in pancreatic cancer. We will utilize the PROMIS-29, and FACT-Hepatobiliary survey tools [43-45]. They are both validated in patients with pancreatic cancer and will help us understand the benefit of this therapy in our patient population.

Currently, the majority of information upon which oncologists base their treatment decisions is obtained at the time of the patient clinic visit. This data includes the patient's recall of symptoms and physical functioning, in addition to laboratory, imaging and physical exam information. Patient reported data (PRD) can be affected by recall bias [46, 47]. Furthermore, PRD can be influenced by a patient's desire to affect the physician's understanding of their clinical condition. For example,

patients may want their oncologist to believe that they are doing well, so that they may be a candidate for further cancer-directed therapies. Patients may de-emphasize physical symptoms and tolerance to therapy in an attempt to convince themselves that they are doing well. Oncologists rely on the PRD to make their own clinical judgments regarding changes in a patient's clinical condition and therapy choices.

The utilization of wearable biometric sensors may allow an inexpensive method of acquiring objective clinical data. Currently, off-the-shelf technology is being used commercially to track fitness. These wrist-worn devices can provide real-time data relating to movement, altitude, heart rate, body composition, temperature, and sleep quality. We will use the wearable activity monitor (e.g., Fitbit Charge HR) to assess activity in patients with pancreatic cancer and determine whether that activity correlates with changes in cachexia, functional status and PROs (i.e.PROMIS-29 and FAACT) around functional domains of quality of life [48-50]. Data collected may support the efficacy of this therapeutic intervention and influence the development of additional patient-centric, meaningful endpoints for future therapeutic trials around exocrine pancreatic insufficiency.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Feasibility to complete pancreatic enzyme replacement therapy during the first 8 weeks of the study

2.2 Secondary Objectives

2.2.1 Measure weight stability at baseline and day 1 of every cycle for 6 months

2.2.2 Record 24-hour caloric intake at C1D1, C3D1, and end-of-study

2.2.3 Assess stool frequency at C1D1 and C3D1

2.2.4 Stool consistency at C1D1 and C3D1

2.2.5 Measurement of fat-soluble vitamins at baseline and end-of-study

2.2.6 Evaluate microbiome at C1D1 and C3D1

2.2.7 Determine if pancreatic enzyme replacement therapy is associated with increased daily activity (steps, counts, stairs, sleep, heart rate, active minutes) using a wrist-worn fitness tracker (e.g., Fitbit)

2.3 Patient-Reported Outcomes / Exploratory Objectives

2.3.1 To assess quality of life including pain assessment using PROMIS-29 at baseline and day 1 of every cycle for 6 months

2.3.2 To assess patient-reported response to therapy using FAACT (Functional Assessment of Anorexia/Cachexia Therapy) baseline and day 1 of every cycle for 6 months

2.3.3 Measure fecal elastase at baseline

2.3.4 Assess overall survival

2.3.5 Assess adverse events for safety and tolerability

2.3.6 Assess inflammatory biomarkers in research blood

2.3.7 Assess the presence of frailty phenotype

2.3.8 Assess body composition using computed tomography collected as standard of care every 8 weeks

2.4 Study Hypotheses

2.4.1 Primary Hypothesis

Pancreatic enzyme supplementation in addition to standard of care treatment is feasible for patients to follow for at least 8 weeks.

2.4.2 Secondary Hypotheses

Pancreatic enzyme supplementation in addition to standard of care treatment will stabilize weight loss in patients with borderline resectable, locally advanced, and advanced pancreatic cancer patients with exocrine pancreatic insufficiency.

Pancreatic enzyme supplementation, in addition to standard of care chemotherapy and dietitian consultation, will:

- Increase caloric intake
- Make stool frequency more consistent
- Improve stool consistency
- Improve levels of fat-soluble vitamins
- Alter the microbiome favorably
- Increase daily activity

2.4.3 Exploratory Hypotheses

- Improve quality of life and symptoms of pain from baseline
- Patient-reported response the therapy will improve

- Fecal elastase may correlate with response to pancreatic enzyme supplementation
- Survival and response rate may benefit from a comprehensive approach to nutritional support
- Pancreatic enzyme supplementation will be safe and tolerable
- Weight loss and cachexia may be associated with genomic and stromal alterations in the tumor.
- Inflammatory biomarkers may be improved
- The frailty phenotype may be improved
- Lean body mass may be maintained throughout treatment course

2.5 Endpoints

2.5.1 Primary endpoint

- Measure patient compliance to take pancreatic enzyme replacement therapy using a patient reported Pancreaze daily accountability log. Patient compliance will be defined as patients taking ≥ 50 % of the needed total lipase units. The primary endpoint will be met if at least 50% of the subjects in each cohort take at least 50% of the total needed lipase units within the first 8 weeks of treatment.

2.5.2 Secondary endpoints

- Measure weight stability at baseline and day 1 of every cycle for 6 months
- Food intake will be assessed by study staff at C1D1, C3D1, and end-of-study. A validated 24-hour recall questionnaire will be analyzed using the automated self-administered 24-hour Dietary Assessment tool (ASA-24)
- Assess stool frequency at C1D1 and C3D1 using a stool survey
- Stool consistency at C1D1 and C3D1
- Measurement fat-soluble vitamins (including Vitamins A, D, E, and K) at baseline and end-of-study
- Evaluate microbiome at C1D1 and C3D1
- Activity (steps taken, stairs climbed, sleep duration and disturbances, heart rate and intensity) will be collected using the wearable activity monitor (e.g., Fitbit Charge HR) daily for the duration of the study.

2.5.3 Exploratory endpoints

- Quality of life and symptoms of pain will be measured using the PROMIS-29 at baseline and day 1 of every cycle for 6 months
- Patient-reported response the therapy will be measured using FAACT at baseline and day 1 of every cycle for 6 months

- Measure fecal elastase at baseline
- Survival will be evaluated at every visit and every 6 months during 36-month follow-up
- Safety and tolerability will be assessed by collecting adverse events throughout the study
- Research blood will be assessed for inflammatory biomarkers including: IL-6, interferon 1-alpha, TNF-alpha, Interleukin-1β, neuropeptide y, ZAG, ghrelin, CCK, GLP-1, PYY, glucagon and insulin at baseline and day 1 of every other cycle for 6 months and at the end-of-study visit. We will use standardized ranges for normal levels of the following assays.
- Presence of frailty phenotype using Fried's definition [50] will be evaluated at baseline and day 1 of every other cycle for 6 months by measuring patient grip strength, using a dynamometer during physical exam, a 15 foot walk test, question about energy levels and activity (APPENDIX E)
- Assess body composition using computed tomography collected as standard of care every 8 weeks

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Borderline resectable, locally advanced, and advanced pancreatic cancer patients (can include new or recurrent diagnosis) referred to SOCCI-CSMC

3.1.2 Age ≥ 18 years.

3.1.3 ECOG performance status 0-1 or Karnofsky PS >60% (Appendix A)

3.1.4 Clinical diagnosis of exocrine pancreatic insufficiency

3.1.5 Cachexia defined as ≥5% weight loss in the presence of chronic illness, within any 6-month period prior to screening OR as documented by the medical physician based on standard diagnosis of cachexia

3.1.6 Life expectancy of greater than 3 months, in the opinion of the investigator.

3.1.7 Patients must have normal organ and marrow function as defined below:

Absolute Neutrophil Count (ANC)	≥500/mcL
Platelets	≥50,000/mcL
Total bilirubin	≤ 5X upper limit of normal (ULN)
AST(SGOT)/ALT(SGPT)	≤ 5 X ULN
Creatinine OR creatinine clearance	≤ 3 times the upper limit of normal OR ≥ 30 mL/min/1.73 m^2 for patients with creatinine levels above normal.

Note: Patients with biliary stents are eligible provided that all other inclusion criteria are met.

3.1.8 Woman of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from the time of signing the informed consent form, for the duration of study participation, and for at least 30 days after discontinuing from study treatment.

3.1.9 Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

3.2.1 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.2 Women who are pregnant or are breastfeeding

3.2.3 Dementia or altered mental status that would prohibit the understanding or rendering of informed consent

3.2.4 Unable to swallow intact capsules

3.2.5 Fibrosing colonopathy: Patients with history of fibrosing colonopathy have been reported to experience advancement to colonic strictures with doses of lipase>6000 units/kg/meal over prolonged periods of time.

3.2.6 History of chronic illness associated with malabsorption or nutrient deficiency including but not limited to chronic pancreatitis, cystic fibrosis, celiac disease, Crohn's disease, pernicious anemia and/or prior intestinal resection.

3.2.7 Pregnancy, breastfeeding, or of childbearing potential and not willing to use methods of birth control during the study

3.2.8 Active drug abuse or intoxication with any substance including alcohol (blood alcohol content >0.08%, legal driving limit)

3.2.9 Known allergy to any of the active ingredients in pancreatic enzyme supplementation

3.2.10 Concurrent use of pancreatic enzyme supplementation or over the counter supplements which contain lipase, protease, and amylase as active ingredients

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 Agent Administration

Treatment will be administered on an outpatient basis. The investigational treatment cycle is every 4 weeks. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Subjects meeting enrollment criteria will be given Pancreaze (84,000 lipase units per main meal and 42,000 lipase units per snack). Subjects will undergo treatment with pancreatic enzymes indefinitely as per standard therapy for patients with EPI. If symptoms and signs of steatorrhea persist, the dosage may be increased by the healthcare professional.

If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age. Patients currently receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

Subjects will be instructed to take 84,000 units (4 capsules) per main meal and 42,000 units (2 capsules) per snack. Should dose reductions be required per treating investigator, the guidelines in Section 4.1.3 will be followed.

4.1.2 Drug Interactions

No drug interactions have been identified. No formal interaction studies have been conducted.

Patients taking fat-soluble vitamin supplements will be advised to discontinue use while on this trial as it is likely to interfere with the proposed study assessments.

4.1.3 Dosing Delays / Modifications

Treatment is administered according to the Time & Events Table (Section 5.6). Treatment will be delivered over 4-week cycles (1 cycle=28 days). Data will also be collected for patients that receive titrated dosing per investigator's discretion and following Table 1.

Toxicity will be evaluated using the NCI Common Terminology Criteria for Adverse Events, Version 4.0. The frequency of toxicities per organ system will be tabulated using descriptive statistics. All patients who receive any amount of the study drug will be evaluable for toxicity.

Subjects will be instructed to take 84,000 units (4 capsules) per main meal and 42,000 units (2 capsules) per snack. Should dose reductions be required per treating investigator, the following guidelines will be followed:

Table 1. Dose modifications

	Per meal	Per snack
Starting dose	84,000 USP units of lipase (4 capsules)	42,000 USP units of lipase (2 capsules)
Dose modification 1	63,000 USP units of lipase (3 capsules)	21,000 USP units of lipase (1 capsule)
Dose modification 2	42,000 USP units of lipase (2 capsules)	21,000 USP units of lipase (1 capsule)

Any dose modifications will be recorded in the research record, including dates. Compliance will be calculated based on the recommended dose.

4.1.4 Duration of Therapy

The patients will be followed on treatment for the 24-week study treatment period. Treatment may continue per SOC until death or until any of the following occur:

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

In the absence of the above criteria, subjects may continue to receive study treatment at the investigator's discretion.

4.2 Concomitant Medications

Concurrent use of other pancreatic enzyme supplementation, fat-soluble vitamin supplements, or over the counter supplements which contain lipase, protease, and amylase as active ingredients is not permitted.

Only conmeds that are used to treat an adverse event deemed at least possibly related to Pancreaze need to be recorded in the REDCap database.

4.3 Duration of Follow-up

Patients will undergo an End of Study assessment 30 days after completion of the 24-week study treatment period. Patients removed from treatment for unacceptable adverse events will then be followed until resolution or stabilization of the adverse event and will continue to be followed for the duration of the study as per protocol. After the End of Study Assessment, follow-up will involve every 6-month phone calls to collect survival data for 36 months.

4.4 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.7 apply.

4.5 Subject Replacement

Subjects who withdraw from the study treatment will be replaced.

5.0 STUDY PROCEDURES

5.1 List of Study Procedures

5.1.1 Informed Consent – must be obtained within 6 weeks of Day 1

5.1.2 Review subject eligibility criteria

5.1.3 Pregnancy test

Pregnancy test for women of child-bearing potential as per standard of care.

5.1.4 Demographics

Age, gender, race, and ethnicity

5.1.5 Medical/surgical history

Complete medical and surgical history, history of infections

5.1.6 Physical exam including *vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height (at screening/baseline only), weight

5.1.7 Performance status

Performance status evaluated prior to study entry according to Eastern Cooperative Oncology Group (ECOG) or Karnofsky performance status criteria (Appendix A)

5.1.8 Standard of care CT imaging

As indicated per standard of care, approximately every 8 weeks

5.1.9 Adverse event assessment

Signs/symptoms present at baseline prior to treatment initiation will be recorded as medical history. Adverse events will be assessed from time of treatment initiation for the duration of the study treatment period until the end-of-study visit. See Section 6 for Adverse Event monitoring and reporting.

5.1.10 Review previous and concomitant medications

5.1.11 Blood collection for general health assessment

CBC with differential, CMP, Phosphorus, Magnesium. Phosphorus and Magnesium will be assessed at C1D1 only.

5.1.12 Blood draw for tumor assessment

CA-19-9, C-reactive protein (CRP). CRP will be assessed at C1D1 only.

5.1.13 Blood draw for fat soluble vitamin levels

Serum levels of Vitamins A (serum retinol), D (25-Hydroxy), E (serum alpha-tocopherol), and K (PIVKA-II and prothrombin time).

5.1.14 Research blood draw

See Section 7.0 for details. 8 hour fast is required. Morning blood draw is required.

5.1.15 Stool sample

A stool collection kit will be given to the patient during physical exam, where patient will be advised to follow instructions on kit and bring their sample into laboratory as

instructed (see Sections 5.2 and 5.3.2). Microbiome analysis and fecal elastase will be measured from collection of stool sample (Section 8). Fecal elastase will be measured at baseline only.

5.1.16 Hand grip and 15 ft walk test

Hand grip using the hand-held dynanometer. Three assessments for each hand will be completed and recorded. A timed walk-test from first foot fall to last foot fall over 15 feet will be performed twice per assessment.

5.1.17 Bionutrition assessment

ASA-24 (24-hour food recall) and taste and smell alteration. ASA-24 is completed electronically and may be completed within 7 days of the study visit.

5.1.18 Patient reported outcomes

Patient reported outcomes (Quality-of-life questionnaire: PROMIS-29; FAACT)

5.1.19 Self-reported daily Pancreaze accountability log and compliance calculation

Subjects will record usage of Pancreaze in a daily log. Subjects will return log to study staff at study visits for compliance calculation.

5.1.20 Activity Monitoring

Wearable activity monitor (e.g., Fitbit Charge HR) activity monitoring to measure step count, heart rate, activity intensity, stairs climbed and sleep. Provide wearable activity monitor with charger and instructions for activity monitoring. Wearable activity monitor will be paired to the subject's personal smartphone. Subject may keep or return the wearable activity monitor at the end-of-study visit. Continued collection of activity monitor data during follow-up will be optional.

5.1.21 Survival follow-up

Per Section 5.5.

5.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures used for eligibility verification must be performed **within 4 weeks of Day 1** unless otherwise stated. Baseline procedures not required for eligibility verification can occur on Cycle 1, Day 1 of treatment (See section 5.3).

The screening and baseline procedures include:

- Informed consent
- Eligibility review, including:
  - Pregnancy test
- Demographics
- Medical/Surgical history
- Complete physical exam
- Standard of care CT imaging
- Height, weight, vital signs
- Performance status (ECOG or Karnofsky)
- AE (baseline symptom) assessment

- Concomitant medications review
- Labs: CBC/diff, CMP
- Blood draw for fat soluble vitamin levels
- Fecal elastase
    - Note: for maximum flexibility for the patients, the fecal elastase stool sample may be collected during screening or until C1D1 (+ 7 days). Patients will be encouraged to provide the fecal elastase stool sample prior to starting treatment, if possible.

5.3 Procedures During Treatment

These visits can occur within a window of -/+ 7 business days of the anticipated visit date to account for clinic closures or holidays and to align with the standard of care chemotherapy administration schedule.

5.3.1 *Day 1 of Every Cycle (each 4 weeks/28 days)*

- Treatment as per dosing schedule
- Completion of study dosing diary - for the first two cycles only
- Safety evaluation (As per CTCAE grading)
- Physical Exam
- Weight
- Vital signs
- ECOG or Karnofsky performance status (Appendix A)
- Concomitant medications
- Blood collection (CBC with differential, CMP)
- CMP add-ons (Phos, Mag) (C1D1 only)
- Tumor markers (CA 19-9)
- CRP (C1D1 only)
- Assess wearable activity monitor functionality

5.3.2 *Day 1 of Every Other Cycle (every 8 weeks)*

- Research blood (See Section 7). 8 hour fast is required. Morning blood draw is required.
- Self-administered QOL surveys: PROMIS-29, FAACT (APPENDICES C, D)
- Frailty status (hand grip; 15 ft walk-test – Appendix E)
- Bionutrition assessment (ASA-24 +taste and smell alteration) conducted by study staff (Appendix B) (C1D1, C3D1 only)
- Stool sample for microbiome analysis (Section 8) (C1D1 and C3D1 only)
    - Note: for maximum flexibility for the patients, the C1D1 microbiome stool sample may be collected during screening or until C1D1 (+ 7 days). Patients will be encouraged to provide the microbiome stool sample prior to starting treatment if possible. If collected during screening, the microbiome sample will be stored until eligibility is confirmed; if the patient results in a screen fail, the sample will be destroyed unless consent is granted for its use on another IRB-approved protocol, e.g., GI-Bank protocol (IRB# Pro00054363).
    - Note: for maximum flexibility for the patients, the C3D1 microbiome stool sample may be collected +/- 7 days of C3D1.
- Stool survey (C1D1 and C3D1 only)

5.3.3 End-of-Treatment Visit (EOT), +7 days.

Subjects will continue to take the study drug until the Cycle 6 Day 28 time point. Subjects should be reminded to discontinue study supply of Pancreaze following Cycle 6 Day 28. Up to seven days following the last dose, there will be an EOT visit for subjects to return pill bottles and to transition to SoC enzymes, if applicable.

- Safety evaluation (As per CTCAE grading)
- Return pill bottles
- Transition to SoC enzymes (if applicable)

5.3.4 Standard of care CT imaging

As indicated per standard of care, approximately every 8 weeks

5.4 End-of-Study Visit

- The End-of-Study visit is to occur 30 days following last dose of study treatment, +/- 7 days.
- Research blood (See Section 7). 8 hour fast is required. Morning blood draw is required.
- Safety evaluation (As per CTCAE grading)
- Physical Exam
- Weight
- Vital signs
- ECOG or Karnofsky performance status (Appendix A)
- Concomitant medications
- Blood collection (CBC with differential, CMP)
- Tumor markers (CA 19-9)
- Fat soluble vitamin levels
- Frailty status (hand grip; 15 ft walk-test – Appendix E)
- Bionutrition assessment (ASA-24 +taste and smell alteration) conducted by study staff (Appendix B)
- Self-administered QOL surveys: PROMIS-29, FAACT (APPENDICES C, D)
- Assess wearable activity monitor functionality

5.5 Follow-up Procedures

Patients will be followed every 6 months for 36 months after completion of (or early withdrawal from) study treatment or until death.

If there is no record of patient survival in medical chart by review, a phone call will be made to assess survival. Physical exam, weight, vital signs, and ECOG or Karnofsky performance status will also be collected from the medical record if available per standard of care.

5.6 Time and Events Table

Procedures	Screening / Baseline	Treatment		Follow-up Phase	
	Within 4 weeks of Day 1	**Every Cycle (Every 4 weeks)** Cycles 1, 2, 3, 4, 5, 6 (Weeks 0, 4, 8, 12, 16, 20) Day 1 (+/- 7 days)	**End of Treatment[9]** End of Week 24 (+ 7 days)	**End-of-Study Visit** 30 days after treatment termination (+/- 7 days)	Survival Follow-up Every 6 months for 36 months (+/7 days)
Informed Consent	X				
Eligibility review	X				
Pregnancy test	X				
Demographics	X				
Medical / Surgical History	X				
Complete Physical Exam	X	X		X	X
Standard of Care CT imaging		As per standard of care, approximately every 8 weeks			
Height	X				
Weight	X	X		X	X
Vital Signs	X	X		X	X
Performance Status (ECOG or Karnofsky)	X	X		X	X
Adverse Event Assessment	X	X	X	X	
Concomitant Medications	X	X		X	
Blood collection (CBC, CMP)	X	X		X	
CMP add-ons (Phos, Mag)		X (C1D1 only)			

Procedures	Screening / Baseline	Treatment		Follow-up Phase	
	Within 4 weeks of Day 1	**Every Cycle (Every 4 weeks)**	**End of Treatment[9]**	**End-of-Study Visit**	Survival Follow-up Every 6 months for 36 months (+/7 days)
		Cycles 1, 2, 3, 4, 5, 6 (Weeks 0, 4, 8, 12, 16, 20)	End of Week 24 (+ 7 days)	30 days after treatment termination (+/- 7 days)	
		Day 1 (+/- 7 days)			
CA 19-9 (biomarker)		X		X	
C-reactive protein (CRP)		X (C1D1 only)			
Fat soluble vitamin levels[5]	X			X	
Research Blood Tests		X[1]		X	
Stool Sample Microbiome and Stool Survey		X (C1D1[7] and C3D1[8] only)			
Fecal elastase	X[7]				
Hand grip and 15 ft walk test		X[1]		X	
Bionutrition assessment: ASA-24 (24-hour food recall)[3]; taste and smell alteration		X (C1D1 and C3D1 only)		X	
Self-administered QOL survey: PROMIS-29; FAACT		X[1]		X	
Pancreaze treatment		X (daily)[6]			
Self-reported daily Pancreaze accountability log and compliance calculation[4]		X			
Physical Activity: Assess wearable activity monitor functionality		X		X	
Wearable activity monitoring		Continuous			X[2]
Return research pill bottles/transition to SOC enzymes			X		

Procedures	Screening / Baseline	Treatment		Follow-up Phase	
	Within 4 weeks of Day 1	**Every Cycle (Every 4 weeks)**	**End of Treatment[9]**	**End-of-Study Visit**	Survival Follow-up Every 6 months for 36 months (+/7 days)
		Cycles 1, 2, 3, 4, 5, 6 (Weeks 0, 4, 8, 12, 16, 20)	End of Week 24 (+ 7 days)	30 days after treatment termination (+/- 7 days)	
		Day 1 (+/- 7 days)			
Survival Follow-up					X

[1]To be completed at baseline and day 1 of every other cycle for 6 months. 8 hour fast is required for all research blood draws, blood draws must be scheduled in the morning, and deviations must be recorded.
[2]Fitness tracking with the wrist-worn wearable activity monitor is optional during follow-up.

[3]ASA-24 is completed electronically and may be completed within 7 days of the visit.
[4]Subjects will complete a daily compliance diary for the first two cycles only. Diary will be given to patients on Day 1 of the first two cycles. Subjects will return diary to study staff for compliance calculation on completion of each of the first two cycles.
[5]Fat-soluble vitamin labs to be drawn include: Vitamin A: serum retinol; Vitamin D:25-Hydroxy; Vitamin E: serum alpha-tocopherol; Vitamin K: PIVKA-II and prothrombin time.
[6]The patients will be followed on treatment for the 24-week study treatment period. Treatment may continue beyond the study treatment period, at the physician's discretion, per standard of care. Pancreaze will be dispensed at C1D1 and C4D1, and subjects will return remaining supply at C4D1 and the end-of-treatment visit for drug accountability by Research Pharmacy.
[7]Stool sample may be collected during screening or until C1D1 + 7 days.
[8] Window for C3D1 sample is +/- 7 days.
[9]Subjects will continue to take the study drug until the Cycle 6 Day 28 time point. Subjects should be reminded to discontinue study supply of Pancreaze following Cycle 6 Day 28.

5.7 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.7.1 Patient voluntarily withdraws (follow-up permitted);

5.7.2 Patient withdraws consent (termination of treatment and follow-up);

5.7.3 Patient is unable to comply with protocol requirements;

5.7.4 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.7.5 Treating physician judges continuation on the study would not be in the patient's best interest;

5.7.6 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.7.7 Lost to follow-up. *If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All reasonable efforts must be made to locate subjects to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter.*

All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

6.0 ADVERSE EVENTS

6.1 Adverse Event Monitoring

The investigator or designee is responsible for ensuring that adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has initiated treatment and until the 30-day end-of-study visit, are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE) - Descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting.
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity
- Grade of toxicity
- Attribution of relatedness to the investigational agent- (this must be assigned by an Investigator, sub-investigator, or treating physician)

- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline
- any abnormal laboratory values have returned to baseline
- there is a satisfactory explanation other than the study drug for the changes observed, or
- death

6.2 Protocol-specific Adverse Event Monitoring Guidelines

Since this supplement is FDA approved as part of standard of care in the patient population under study, only AEs of interest, as outlined below, will be collected and recorded in the EDC:

• Any event deemed serious and expected OR unexpected, regardless of cause.

AND

- AEs of interest included below:

Expected toxicities to Pancreaze
Abdominal pain
Abdominal pain upper
Flatulence
Diarrhea
Abnormal feces
Fatigue

Note; All expected toxicities from chemotherapy can be found in the FDA approved Package Insert.

6.3 Definitions

6.3.1 Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). AE's will be collected once the consent is signed and treatment is initiated.

6.3.2 Serious Adverse Events

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

6.3.2.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

6.3.2.2 Is life-threatening.

The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

6.3.2.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

6.3.2.4 Results in persistent or significant disability or incapacity.

6.3.2.5 Is a congenital anomaly/birth defect

6.3.2.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event.“

Medical events may include, but are not limited to: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

6.3.3 Unanticipated Problem (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known to an individual or group of individuals (including research subjects, research staff, or others not directly involved in the research).

6.3.4 Evaluable for toxicity

Any patient who receives at least one dose of study drug is evaluable for toxicity and will be included in the safety analysis.

6.4 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common

Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at http://ctep.cancer.gov/reporting/ctc.html.

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

6.5 Reporting Requirements for Adverse Events

6.6 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol-defined treatment. Any event that occurs more than 30 days after the last dose of protocol-defined treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected when either the type of event or the severity of the event is not listed in the current known adverse events listed in the package insert.

6.6.1 Expedited Reporting

6.6.1.1 Reporting to the Principal Investigator

The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last protocol-defined administration of the study drug.

PI Phone Number for Expedited Reporting:
Andrew Hendifar, MD (310) 423-2217

Alternate Phone Number for Expedited Reporting:
Jun Gong (310) 423-5776

6.6.1.2 Reporting to the DSMC

Serious Adverse Events deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g. due to disease progression) to be reported to the DSMC within 24 hours of awareness for medical monitor ad hoc review between meetings to determine if immediate action is required. Reports to be emailed to the DSMC team at GroupSOCCICCTODSMCAdmin@cshs.org.

6.6.1.3 Reporting to the Institutional Review Board (IRB)

The IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others."

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

6.6.1.4 Reporting to the External Funding Source (Vivus)

All SAEs to be forwarded to Vivus within 24 hours of awareness. This will allow Vivus to cross report to other clinical trials/investigators in a timely manner. Vivus may request additional or supportive information to clarify details in a follow-up report and will submit request to the site in writing.

Reports should be submitted to: GPV@vivus.com

7.0 CORRELATIVES/SPECIAL STUDIES

7.1 Research Blood Collection Kit and Instructions

Patients will be instructed to fast for at least 8 hours prior to research blood draws and blood draws must be scheduled in the morning. Deviations from this must be recorded. This Kit is for collection, processing, storage and/or shipping of serum, plasma, or whole blood (as specified by the protocol):

Kit contents:

- One (1) 5 – 10 cc Red Top tube for serum (A)

- One (1) 5 – 10 cc Lavender Top EDTA preserved with anticoagulant tube for plasma (B)
- One (1) 5 – 10 cc Lavender Top EDTA preserved with anticoagulant tube for Whole Blood (C)
- Fifteen (15) to thirty (30) 1 ml cryovials
- Pipettes
- Two (2) patient-specific cryovial storage boxes
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Lab Requisition Form and Kit Instructions

7.1.1 Preparation and processing of serum, plasma, and whole blood

7.1.2 Serum: Red Top Tube

- Label as many 1ml cryovials (up to 5-10) as necessary for the serum collected. Label them with:
  - Study name: PanCax3
  - Subject ID
  - Patient initials (First, Middle, Last)
  - Collection date (Month, Day, Year)
  - Serum cryovial number (e.g., S1, S2, S3, S4, S5, etc…)

7.1.2.1 Process

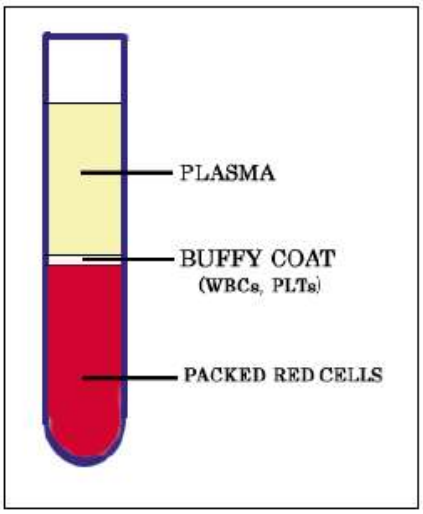
- Transport Red Top Tube for processing at room temperature
- Allow the blood to clot by leaving it undisturbed at room temperature (15-30 minutes)
- Centrifuge at 1,000 x g for 10 minutes in a refrigerated centrifuge (4°C). If unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the Lab Requisition Form.
- Aliquot 0.5 ml serum into as many 1 ml cryovials (up to 5-10) as are necessary for the serum collected and stored at -80°C. Ensure the patient initials, collection date and serum cryovial number (e.g., S1, S2, S3, S4, S5, etc…) are marked on the cryovials.
- Place cryovials into the patient-specific cryovial storage box and immediately freeze at -70 to -90° C, and store frozen until ready to ship/transfer. See below for storage conditions.

7.1.3 Plasma: Lavender Top EDTA tube #1

- Label as many 1ml cryovials (up to 5-10) as necessary for the plasma collected. Label them with:
  - Study name: PanCax3
  - Subject ID
  - Patient initials (First, Middle, Last)
  - Collection date (Month, Day, Year)
  - Plasma cryovial number (e.g., P1, P2, P3, P4, P5, etc…)

7.1.3.1 Process

- After collection, invert tube(s) twice to ensure adequate mixing of EDTA.
- Centrifuge specimen(s) within one hour of collection at 2,000 x g for 15 minutes in a refrigerated centrifuge (4°C). If unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the Lab Requisition Form.
- If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
- Aliquot 0.5 ml plasma into as many 1 ml cryovials (up to 5-10) as are necessary for the plasma collected and stored at -80°C. Ensure the patient initials, collection date and plasma cryovial number (e.g., P1, P2, P3, P4, P5, etc…) are marked on the cryovials.
- Place cryovials into the patient-specific cryovial storage box and immediately freeze at -70 to -90° C, and store frozen until ready to ship/transfer. See below for storage conditions.



7.1.4 Whole Blood: Lavender Top EDTA tub #2

Label as many 1ml cryovials (up to 5-10) as necessary for the whole blood collected. Label them with:

- Study name: PanCax3
- Subject ID
- Patient initials (First, Middle, Last)
- Collection date (Month, Day, Year)
- Whole blood cryovial number (e.g., WB1, WB2, WB3, WB4, WB5, etc…)

7.1.4.1 Process

- After collection, invert tube(s) twice to ensure adequate mixing of EDTA.
- Blood can also be mixed for 5 minutes on a mixer at room temperature.
- Aliquot 0.5 ml blood into as many 1 ml cryovials (up to 5-10) as are necessary for the whole blood collected and stored at -80°C. Ensure the

patient initials, collection date and whole blood cryovial number (e.g., WB1, WB2, WB3, WB4, WB5, etc…) are marked on the cryovials.
- Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship/transfer. See below for storage conditions.

7.1.5 All Blood Samples – Freezing and Storage

- Freeze all blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- Store at –80°C (-70°C to -90°C) until ready to transfer.
- If a -80°C Freezer is not available,
- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week; OR
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily; OR
- Samples can be stored in liquid nitrogen vapor phase
- Please indicate on Lab Requisition the storage conditions used and time stored.

8.0 FECAL SPECIMEN COLLECTION

8.1 Materials

- Toilet hat
- Collection bucket
- Gloves
- Sterile container with scooper attached to cap
- Biohazard laboratory bags (2)
- Post-it to record collection date and time
- Styrofoam ice box
- Ice packs

8.2 Home Instructions (see Appendix H)

8.3 Storage of stool sample

The sample should be frozen until transport to the visit. The specimen should be transported frozen and kept frozen upon delivering specimen. Upon receipt of the sample at the investigator site – site personnel should verify that the collection date and subject ID is written on the paper. Stool specimens will be submitted to the CCTO laboratory for documentation and temporary storage in -20^{o}C or -80^{o}C.

9.0 STATISTICAL CONSIDERATIONS

9.1 Power Assessment

The primary hypothesis to be tested is whether the percentage of patients who complete the course of pancreatic enzyme replacement therapy at 8 weeks is at least 50% for each of the three cancer stage subgroups: borderline resectable, locally advanced and advanced pancreatic cancer. We assumed a sample size equal to 10 patients for each group. The minimum detectable difference from the proportion 0.5 is 0.417 using a Binomial Exact test with Bonferroni correction. Thus, we will declare the sustainability of the therapy if 9 or more patients complete the treatment for each subgroup.

9.2 Data Analysis Plan

The primary hypothesis to be tested is whether is the percentage of patients who complete the pancreatic enzyme replacement therapy at 8 weeks is at least 50% for each of the three cancer stage subgroups: borderline resectable, locally advanced and advanced pancreatic cancer. A 95% confidence interval [1] for the proportion of treatment completeness will be calculated for each cancer stage. The statistical analysis will be performed in three steps for all secondary endpoints: 1) Descriptive analysis: Measures of central tendency (mean, median and mode), measures of variability (standard deviation, range and quantiles). Standard distribution plots such as profiles-plots for repeated measures and box-plots will be constructed to examine the distribution of the data. 2) Univariable Analysis and 3) Multivariable analysis: The linear regression model will be applied to explain the secondary endpoints as a function of the patient's baseline variables. Assumptions of the linear regression model will be examined. If the assumptions are not met, Generalized Additive models for Location, Scale and Shape (GAMLSS) which provide a general framework for extending a standard linear model will be applied [2]. The goodness of fit for each model will be accessed through a residual analysis using Worm-plots [51] and variable selection will be performed as outlined by Harrell [4]. Random effects will be added to describe the repeated measures. In addition, overall survival curve will be estimated using the Kaplan-Meier method with 95% confidence interval. All tests of hypotheses will be two-sided and a significance level of 0.05 and calculations will be performed using R, version 3.2.3 [5].

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient’s participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Registration Procedures

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects that do not pass the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as

determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the Principal Investigator (PI). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study team will track all subjects who sign consent using OnCore. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using a three-digit numeric ID that follows the standard SOCCI format (001, 002, etc.).

A) Eligibility Verification

Prior to registration, all subjects must undergo eligibility verification by SOCCI Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC). The following documents will be organized into an eligibility packet, scanned as a pdf, and emailed to GroupSOCCICROQMC@cshs.org for review:

- Registration form (or equivalent), if applicable
- Copy of applicable source documents
- QMC-approved eligibility checklist (signed by investigator and 2 members of the study team)
- Signed patient consent form with Subject's Bill of Rights, HIPAA authorization form, consent progress note, and any optional consent forms, as applicable

B) Registration

After eligibility is verified, registration is completed as follows:

- Assign a patient study number
- Enter the patient in OnCore
- Notify the investigational pharmacy and treating physicians that a subject has gone on study and anticipated treatment start date

Oversight by the principal investigator is required throughout the entire registration process

10.4 Data and Safety Monitoring

10.4.1 Data Monitoring and Quality Assurance

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group (DRG) meetings or equivalent. In addition, the SOCCI Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct internal monitoring visits and audits for data quality and protocol adherence. QMC reports will be forwarded to the SOCCI Data and Safety Monitoring (DSMC). Refer to the DSMC Charter for more details. For any protocol, QMC has the authority to request more frequent reviews or focused safety monitoring if it is deemed appropriate for any reason.

QMC will also conduct the following:

1. Central eligibility verification for all subjects enrolled as described in protocol section 10.3.
2. Central review by the SOCCI CCTO Medical Director or designee of all eligibility exception requests and waiver requests to assess appropriateness to ensure quality data and subject safety protections for investigator-initiated research

10.4.2 Safety Monitoring

Oversight of the progress and safety of the study will be provided by the PI. The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. Adverse events and unanticipated problems are not expected, but if they occur they will be documented and reported according to CS-IRB policies and procedures. If the PI becomes aware of any new safety information that may place subjects at increased risk than what was previously known the IRB will be promptly notified and if warranted, enrollment may be held until the PI determines whether a modification to the study is necessary and/or the informed consent documents are updated accordingly. It is the responsibility of the principal investigator to adhere to the Data Safety Monitoring Plan throughout the life of the study.

In addition, this protocol will utilize the SOCCI Data and Safety Monitoring Committee will provide another layer of data and safety oversight. DSMC membership and responsibilities are governed by the committee charter. Every six (6) months the DSMC findings and recommendations will be reported in writing to the Principal Investigator as a summary letter which will be forwarded by the Principal Investigator or designee to the CS-IRB. The DSMC may increase or decrease the frequency of study review, at their discretion. Refer to the DSMC Charter for details of the DSMC review.

10.5 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file per institutional guidelines.

10.6 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the SOCCI Medical Director and CSMC IRB, the study shall be conducted exactly as described in the approved protocol.

10.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 10 days from the investigator’s awareness of the event.

10.6.2 Protocol Exceptions and Eligibility Waivers

A protocol exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the IRB Policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.* A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical in nature and/or impact an eligibility criterion, affect timing of study drug administration, or the investigator assesses the event may impact subject safety and/or study integrity, may not be implemented without prior approval from the SOCCI (CCTO) Medical Director and the IRB. The PI or her/his designee is responsible for submitting a protocol exception and its supporting documents to the SOCCI CCTO Medical Director for review and further instructions on IRB reporting.

Study team should refer to the IRB *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement* guidelines to determine which deviations and exception requests meet reporting guidelines. Once approved by the medical director, the deviation or exception request must be submitted to the IRB for review and approval prior to implementation.

Special considerations for Eligibility Waivers (EW)
In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be forwarded to the SOCCI CCTO Medical Director for assessment prior to submission to the IRB for approval.

The CCTO Medical Director will review the case and contact the investigator if additional information is needed or further discussion is warranted. The CCTO Medical Director will provide a written assessment/recommended course of action. The CCTO Medical Director's assessment must be uploaded into CS-IRB with the waiver request for IRB review and consideration. The CCTO Medical Director may recommend future protocol changes.

Eligibility Waiver and Exception Request Submission Process
The PI and/or treating physician will provide a written request for an eligibility waiver including case history and justification for prospective deviation from the study design, to the SOCCI CCTO Medical Director. The "IIT Monitoring – Eligibility Waivers and Exception Requests (EW/ER) Form" must be completed then submitted, along with any applicable supporting documents, by email to QMC (GroupSOCCICROQMC@cshs.org) to request an eligibility exception or waiver request from the CCTO Medical Director. This is only a requirement for studies with a DSM category of moderate or high. An assessment from the CCTO Medical Director or designee must be done prior to submission to the IRB for review.

10.6.3 Other Protocol Deviations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety or study integrity. Such planned deviations that do meet this definition and do not affect the subject's safety or study integrity should be noted in the

subject's research record or deviation log as described in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI CCTO's Standard Operating Procedure 12: *Deviation and Noncompliance Reporting*. In this case, a Protocol Deviation report must be submitted in CS-IRB, per IRB policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement*. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

10.6.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

10.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

APPENDIX A: Performance Status Scales

ECOG Performance Status

SCORE	DESCRIPTION
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, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Karnofsky Performance Status Scale

KARNOFSKY PERFORMANCE STATUS SCALE

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

NOTE: APPENDICES B-D ARE UPLOADED AS SEPARATE DOCUMENTS WITHIN THE IRB APPLICATION

APPENDIX E: Measures of Frailty phenotype

Table 1. Operationalizing a Phenotype of Frailty

A. *Characteristics of Frailty*	B. *Cardiovascular Health Study Measure**
Shrinking: Weight loss (unintentional) Sarcopenia (loss of muscle mass)	Baseline: >10 lbs lost unintentionally in prior year
Weakness	Grip strength: lowest 20% (by gender, body mass index)
Poor endurance; Exhaustion	"Exhaustion" (self-report)
Slowness	Walking time/15 feet: slowest 20% (by gender, height)
Low activity	Kcals/week: lowest 20% males: <383 Kcals/week females: <270 Kcals/week
	C. *Presence of Frailty*
	Positive for frailty phenotype: ≥3 criteria present
	Intermediate or prefrail: 1 or 2 criteria present

Table from Fried et al. 2001

Protocol for frailty criteria*:

D1. Weight loss: Weigh patient and assess for weight loss. Someone who is frail may have unintentional weight loss of ≥ 10 pounds in the prior year.

D2. Gait speed: Time a patient's walk for slowness. Someone who is frail has a decreased walking time as defined by a timed 15-foot walk test (5 meters). The time is adjusted for gender and standing height. Men with a height of <173 cm and women with a height <159 cm who walked 15 feet in >7 sec are considered frail; men >173 cm and women >159 cm who walked 15 feet in >6 sec are considered frail.

D3. Weakness: Weakness is established when there is decreased grip strength measured by a dynamometer with the value adjusted for gender and body mass index (BMI). Men with a BMI <24 are considered frail if the grip strength (kg) is <29, for a BMI of 24.1-28, a man is frail if <30, for a BMI >28 a man is frail if <32. For women, a BMI of <23 is considered frail if the grip strength (kg) is <17, a BMI 23.1-26 is considered frail if <17.3, a BMI of 26.1-29 is considered frail if <18, and a BMI >29 is considered frail if <21.

D4. Physical Activity: Determine if the patient has a low physical activity level. This is established by a weighted score of kilocalories expended per week measured by the Minnesota Leisure Time Activity Questionnaire. The questionnaire asks about activities like daily living, sports and hobbies. Frailty is present when males use <383kcal/week, and females <270 kcal/week.

D5. Frailty Phenotype: Score will be calculated based on presence of each of these characteristics where presence of 1-2 criteria are categorized as prefail, and >=3 criteria categorized as frail.

NOTE: APPENDICES F-H ARE UPLOADED AS SEPARATE DOCUMENTS WITHIN THE IRB APPLICATION

APPENDIX I: SUMMARY OF CHANGES

Amending Protocol Version 1 dated 12SEP2019 to Protocol Version 2 dated 28MAY2020

Study Schema: Stool samples for microbiome analysis will be done at C1D1 and C3D1 only.

Throughout the protocol: Dosage of study agent changed from “IU” to “units”.

Study Summary, Section 1.1. Disease Background, Section 9.1 Power Analysis: Sample size reduced from 45 to 30 subjects (from 15 to 10 per sub-group)

Section 2.5.3 Exploratory endpoints, Section 5 Study Procedures, Section 7.2: Removed genomic sequencing on tissue samples; changed to optional sub-study.

Section 5 Study Procedures:
- Phosphorus, Magnesium, and CRP will be assessed at C1D1 only
- Research stool samples for microbiome analysis will be done at C1D1 and C3D1 only.
- Section 5.6 Time and Events table: Addition of row for Pancreaze treatment
- Bionutritional assessments (ASA-24 and Taste and Smell Alteration surveys) conducted at C1D1, C3D1, and End-of-Study only.
- Addition to footnote 7 to describe dispensing and drug accountability by Research Pharmacy.

Section 6 Adverse Events: Updated per institutional boilerplate language.

Section 6.5.1.4 Reporting to the External Funding Source (Vivus): Updated to require SAE reporting within 24 hours.

Section 10 Study Management: Updated per institutional boilerplate language.

Removal of patient-facing Appendices B-D, F-H, which will be uploaded to IRB application as separate documents.

Amending Protocol Version 2 dated 28MAY2020 to Protocol Version 2.1 dated 02SEP2020

Protocol cover page: Addition of co-investigator Dr. Osipov.

Study Schema and Study Summary: Clarification of study assessment time points.

Secondary Objectives 2.2.2, 2.2.3, 2.2.4, and 2.2.6, and corresponding secondary endpoints in Section 2.5.2: Frequency of assessments updated for consistency with Section 5 Study Procedures.

Section 2.2 Secondary Objectives and Section 2.5 Secondary Endpoints: Secondary objective, hypothesis, and endpoint related to “Assess body composition using computed tomography collected as standard of care” moved to exploratory.

Patient-Reported Outcomes / Exploratory Objectives 2.3.6 deleted for consistency with Section 5 Study Procedures.

Section 10.4.1 Data Monitoring and Quality Assurance, Section 10.4.2 Safety Monitoring, Section 10.6.2 Protocol Exceptions and Eligibility Waivers, and Section 10.6.3 Other Protocol Deviations: Updated in accordance with revised institutional boilerplate language.

Amending Protocol Version 2.1 dated 02SEP2020 to Protocol Version 3 dated 04JAN2021

Assessment of Frailty Phenotype:

- Section 2.5.3 Exploratory endpoints: Correction that frailty phenotype will be assessed every *other* cycle, for consistency with Section 5.3.2 Procedures During Treatment.
- Section 5.6 Time and Events Table: Applied footnote 1 to "Hand grip and 15 ft walk test" to clarify that it is done every *other* cycle, for consistency with Section 5.3.2 Procedures During Treatment.

Stool Samples for Fecal Elastase and Microbiome Analysis:

- Inclusion 3.1.4 and Study Summary: “Abnormal fecal elastase <200 ug E1/g stool” changed to “Clinical diagnosis of exocrine pancreatic insufficiency”
- Section 5.2 Screening/Baseline Procedures: Fecal elastase will not be required for eligibility verification. Added note to allow the fecal elastase sample to be collected during screening or until C1D1 + 3 days; patients will be encouraged to provide the sample prior to starting treatment, if possible.
- Section 5.1.15 Stool sample: Added reference to Section 5.3.2 for stool collection procedures.
- Section 5.3.1 Procedures During Treatment - Day 1 of Every Cycle: For clarity, moved stool sample for microbiome analysis to Section 5.3.2 Day 1 of Every Other Cycle.
- Section 5.3.2 Procedures During Treatment - Day 1 of Every Other Cycle:
    - Added note to allow C1D1 microbiome stool sample to be collected during screening or until C1D1 + 3 days; patients will be encouraged to provide the sample prior to starting treatment, if possible. If the sample is collected during screening and the patient results in a screen fail, the sample will be destroyed unless consent is granted for its use on another IRB approved protocol (i.e., GI-Bank protocol).
    - Added note to allow the C3D1 microbiome stool sample to be collected with a window of +/- 7 days of C3D1.
- Section 5.6 Time and Events Table:
    - Addition of footnote 8 to note the fecal elastase and C1D1 microbiome stool samples may be collected during screening until C1D1 + 3 days.
    - Addition of footnote 9 to note the window of +/- 7 days for the C3D1 microbiome sample.

Other Changes:

- Inclusion 3.1.5: “Cachexia defined as ≥5% weight loss in the past 6 months” revised to “Cachexia defined as ≥5% unexplained weight loss within any 6-month period prior to screening OR as documented by the medical physician based on standard diagnosis of cachexia”.
- Section 5.2 Screening/Baseline Procedures: Correction of timeframe for screening from 6 weeks to 4 weeks prior to Day 1, for consistency with Section 5.6 Time and Events table.
- Section 5.3.2 Procedures During Treatment - Day 1 of Every Other Cycle: Added note that stool survey will be done at C1D1 and C3D1 only, for consistency with Section 5.6 Time and Events Table.
- Appendix B. Taste and Smell Alteration Survey:
    - Removal of item B3.
    - Response option for item B4 (renumbered to B3) corrected.
- Appendix G. Stool Survey:
    - Item 3: Revision to item text and response options for clarity.
    - Removal of items 6-7
    - Revision of item 8 (renumbered to item 6) for clarity.

Amending Protocol Version 3 dated 04JAN2021 to Protocol Version 4 dated 13SEP2021

- Cover page: Removal of co-investigators Nicholas Nissen, MD, Veronica Placencio Hickok, PhD and Haesoo Kim.
- Section 2.5, Primary Endpoint: Clarified the primary endpoint.
- Section 3.1.5, Inclusion Criterion: Clarification of definition of cachexia
- Section 4.2, Concomitant Medications: Added section and specified that only conmeds that are used to treat AEs need to be recorded in REDCap.
- Section 5.3.3, Procedures During Treatment: Clarified study treatment should follow standard chemotherapy schedule
- Section 5.3.31 Study Procedures, Day 1 of Every Cycle: Clarification that the study dosing diary is completed for the first two cycles, rather than the first 8 weeks, for consideration of study visit windows
- Study Procedures: Updated visit window for D1 of each cycle from ±3 to ±7
- Study Procedures: Revised D15 visit schedule to require research activities to occur during the standard chemo visits.
- Section 5.4 End-of-Study Visit and Section 5.6 Time and Events Table. Addition of:
    - *Following the Cycle 6 Day 15 visit, subjects will continue to take the study drug until the Cycle 6 Day 28 time point. Subjects should be reminded to discontinue study supply of Pancreaze following Cycle 6 Day 28. The End-of-Study visit is to occur 30 days following completion of study treatment, +/- 7 days.*
- Section 6.1 Adverse Event Monitoring: Clarification that AE collection begins following initiation of treatment, rather than following informed consent.
- Adverse Event Monitoring: Clarified the study will adhere to CTCAE version 5 for adverse event reporting
- Section 6.2, Protocol-specific Adverse Event Monitoring Guidelines: Added section to specify what adverse events need to be recorded in REDCap.

Amending Protocol v4 dated 13SEP2021 to Protocol v5 dated 17JAN2022

- Page 1, Abbreviations: Added abbreviation for End-of-Treatment (EOT)
- Page 2, Study Schema: Added EOT visit along with procedures. Clarified timing of fat-soluble vitamin measurements.
- Section 3.2, Exclusion Criteria: Removed exclusion criterion 3.2.7- other primary malignancies
- Section 5.3.3, Study Procedures: Addition of an EOT visit after C6D28, where patients will return pill bottles and transition to SoC enzymes, if applicable. The Day 15 visit was removed. The following study procedures will no longer occur at Day 15 of each cycle: PE, ECOG, and CMP/CBC
- Section 5.4, End-of-Study visit: Moved information pertaining to discontinuation of enzyme to section 5.3.3- End-of-Treatment visit.
- Section 5.6, Time and Events Table: Removed the Day 15 visit for each cycle and added an EOT visit. The footnotes were updated to reflect the changes to the study visits.

Amending Protocol v5 dated 17JAN2022 to Protocol v6 dated 14OCT2022

- *Study Title:* Updated the title to reflect that there are 3 cohorts for this study (resectable, locally advanced and advanced pancreatic adenocarcinoma).
- *Sections 2.5.3, 5.1.16, 5.2 and 5.6: Removed the optional archival tissue sub-*study.
- *Section 6.2 Protocol-specific Adverse Event Monitoring Guidelines:* Clarified that all serious adverse events regardless of expectedness or relatedness in addition to AESI need to be collected. Added a table of the expected toxicities for Pancreaze as indicated in the Package Insert.

Amending Protocol v6 dated 14OCT2022 to Protocol v7 dated 18MAY2023

- Update Co-Investigators to include Dr. Sankar
- Increase sample size to 40 patients to allow for replacement of unevaluable patients.