Weight Loss in Patients with Advanced Stage Pancreatic Cancer: Role of Serotonin and Effects of Telotristat Ethyl

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PROTOCOL SIGNATURE PAGE

Evaluation of Chemotherapy Effect on Serotonin Levels & Effect of Telotristat ethyl Treatment for Controlling Weight Loss in Patients with Advanced Stage Pancreatic Cancer

VERSION DATE:

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

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Site Investigator Title

_____

Name of Facility

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Location of Facility (City and State)

_____ ❑ Not Submitting to IRB

Expected IRB Approval Date

SYNOPSIS

TITLE	Weight Loss in Patients with Advanced Stage Pancreatic Cancer: Role of Serotonin and Effects of Telotristat ethyl
SHORT TITLE	Effect on Serotonin Levels & Effect of Telotristat ethyl Treatment for Controlling Weight Loss in Pancreatic Cancer (PDAC)
PHASE	II
OBJECTIVES	**Primary Objective:** **1- Aim # 1 - Group 1 (treatment):** Weight stability after 3 months of telotristat ethyl treatment in patients who have significant weight loss (more than 10% by medical history) prior to the start of treatment. This will be documented as % weight change at 3 months compared to baseline. These patients will be treated with Telotristat ethyl and gemcitabine/nab-paclitaxel combination chemotherapy **2- Aim # 2 - Group 2 (correlative):** Evaluate the change in serum serotonin and 24 hr urine 5-HIAA in patients with advanced PDAC (locally. advanced or metastatic) receiving chemotherapy. In this aim, we will include 40 patients who have stable weight or loss of <10% **Secondary Objectives:** **1-** Evaluate the impact of weight stabilization/gain on patients in Group 1 on performance status, quality of life (QOL), Mid Arm Circumference (MAC) and muscle mass on cross sectional imaging. **2-** Evaluate correlations between changes in serotonin/ 5HIAA levels on radiologic response, weight stability, Mid Arm Circumference (MAC), and muscle mass on cross sectional imaging **3-** Evaluate the relation of baseline serotonin and its metabolite 5-HIAA on weight loss in patients with advanced pancreatic (locally advanced unrespectable/recurrent or metastatic) cancer. For this aim, we will include baseline measurement from patients in Group 1 (N=40) and Group 2 (N=40) **4-** Safety and tolerability of telotristat ethyl with gemcitabine/nab-paclitaxel combination chemotherapy. **5-** Evaluate response rate (RR) assessed per Response Evaluation Criteria In Solid Tumors (RECIST), progression free survival and overall survival in patients receiving telotristat ethyl (Group 1)
STUDY DESIGN	Phase II, single center, double arm trial evaluating efficacy on weight stability of telotristat ethyl in combination with chemotherapy (Group 1) and effects of chemotherapy (Group 2) on 5-HIAA levels in a total of 80 advanced stage PDAC subjects

ELIGIBILITY CRITERIA

Each of the criteria in the checklist that follows must be met in order for a subject to be considered eligible for this study.

Inclusion Criteria

GROUP 1 (Telotristat ethyl **treatment group)**

1- Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2- Weight loss of 10% or more (estimated weight loss by history within 3 months of diagnosis)

3- Age ≥ 18 years at the time of consent.

4- ECOG Performance Status of 0-2 within 14 days prior to registration.

5- Histologic or cytological diagnosis of recurrent or metastatic PDAC who present for first line chemotherapy treatment for metastatic disease.

6- Advanced stage pancreas cancer (locally advanced unresectable, recurrent/metastatic)

7- Measurable disease determined using guidelines of RECIST 1.1. Baseline tumor assessment should be performed using high resolution CT scans or MRI.

8- Prior systemic therapy (adjuvant or neoadjuvant setting are acceptable) if disease progressed or recurred within at least 3 months after treatment

9- Estimated life expectancy of > 12 weeks, as assessed by the site investigator.

10- If sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods) due to unknown risk of teratogenicity

11- Demonstrate adequate organ function as defined in Table 1 below; all screening labs to be obtained within 7 days prior to registration.

12- Prior radiation is allowed if happened more than 2 weeks prior to enrollment

Table 1: Organ Function Requirements

System	Laboratory Value
Hematological	
Hemoglobin	≥ 8 g/dL
Absolute Neutrophil Count (ANC)	≥ 1,200/mm^3
Platelet Count (PLT)	≥ 75,000/mm^3
Renal	
Creatinine	≤ 1.5 mg/dL
Albumin	≥ 2 g/dL
Hepatic	
Bilirubin	≤ 1.5 mg/dL
Aspartate aminotransferase	≤ 3 × ULN

(AST)	or ≤5 xULN in the setting of liver metastases
Alanine aminotransferase (ALT)	≤ 3 × ULN or ≤5 xULN in the setting of liver metastases

Exclusion Criteria for Group 1 (Telotristat ethyl group)

1. Subjects with histology other than adenocarcinoma; Examples include: neuroendocrine tumors, acinar cell cancer, sarcoma or lymphoma of the pancreas
2. Ongoing or active infection
3. Symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia. Symptomatic heart failure (NYHA Class II-IV)
4. Acute or sub-acute intestinal obstruction
5. Ascites
6. Documented and/or symptomatic or known brain or leptomeningeal metastases.
7. Severely immune-compromised (other than being on steroids) including known HIV infection
8. Concurrent active malignancy, other than adequately treated non-melanoma skin cancer, other noninvasive carcinoma, or in situ neoplasm. A subject with previous history of malignancy is eligible, provided that he/she has been disease-free for > 3 years.
9. Breast-feeding or pregnant. Serum pregnancy test for women of child-bearing potential must be performed within 7 days prior to first dose of study treatment
10. Prior autologous or allogeneic organ or tissue transplantation.
11. Known allergy to any of the treatment components
12. Have any condition that does not permit compliance with the study schedule including psychological, geographical, or medical.
13. Not able to swallow inability to take oral medications
14. Patients with chronic constipation

Inclusion Criteria GROUP 2 (Correlative group- Non-Telotristat ethyl)

1- Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2- Stable weight or loss of < 10% by history within 3 months of diagnosis

3- Age ≥ 18 years at the time of consent.

4- ECOG Performance Status of 0-2 within 14 days prior to registration.

	5- Histologic or cytological diagnosis of locally advanced unresectable, recurrent/ metastatic pancreas adenocarcinoma (PDAC) who present for first line chemotherapy treatment for metastatic disease. **6-** Advanced stage pancreas cancer (locally advanced unresectable, recurrent/ metastatic) **7-** Prior systemic therapy (adjuvant or neoadjuvant setting are acceptable) if disease progressed or recurred within at least 3 months after treatment **8-** Estimated life expectancy of > 12 weeks, as assessed by the site investigator. **9-** Prior radiation is allowed if happened more than 2 weeks prior to enrollment **Exclusion Criteria for Group 2 (Non- Telotristat ethyl group)** 1. Subjects with histology other than adenocarcinoma; Examples include: neuroendocrine tumors, acinar cell cancer, sarcoma or lymphoma of the pancreas 2. Ongoing or active infection 3. Acute or sub-acute intestinal obstruction
STATISTICAL CONSIDERATIONS	**Primary Endpoint** **Aim # 1:** Estimated weight loss in PDAC patients is 10 % within 3 months prior to diagnosis. Weight stability is the primary end point. Percentage weight change will be calculated at month 3 relative to baseline, and a weight loss < 5% will be considered as clinical meaningful weight stability. A sample size of 40 achieves 81% power to detect a non-inferiority margin of -5% weight change from baseline using a one-sided Wilcoxon test. We assume the true weight change is 0% and follows normal distribution with standard deviation of 12%. The significance level (alpha) of the test is set at 0.05. **Aim # 2-** This is a descriptive end point to see if we can detect a difference of change in serotonin and 5HIAA levels compared to baseline (before chemotherapy treatment) A sample size of 40 achieves 80% power to detect a mean of paired differences of 0.4 with an estimated standard deviation of differences of 1.0 and with a significance level (alpha) of 0.05000 using a one-sided paired t-test. **Secondary Endpoints** **Aim # 1 and 2:** We propose to check serum serotonin albumin and 24- hr urine 5HIAA levels at baseline and every month when the patient is on chemotherapy and telotristat ethyl treatment for 6 months. We will document the MAC and abdominal muscle size. For QOL, we will use the QOL questionnaire and correlate this to treatment.

	Aim # 3: We will document adverse effects of the treatment using the grading system of the CTCAE version 4 **Aim # 4**: We will correlate response by checking the standard of care scans and evaluating RECIST
TOTAL NUMBER OF SUBJECTS	N = 80 (40 receiving drug)
ESTIMATED ENROLLMENT PERIOD	Estimated 12 months enrollment, follow up for 8 months
ESTIMATED STUDY DURATION	Estimated 20 months

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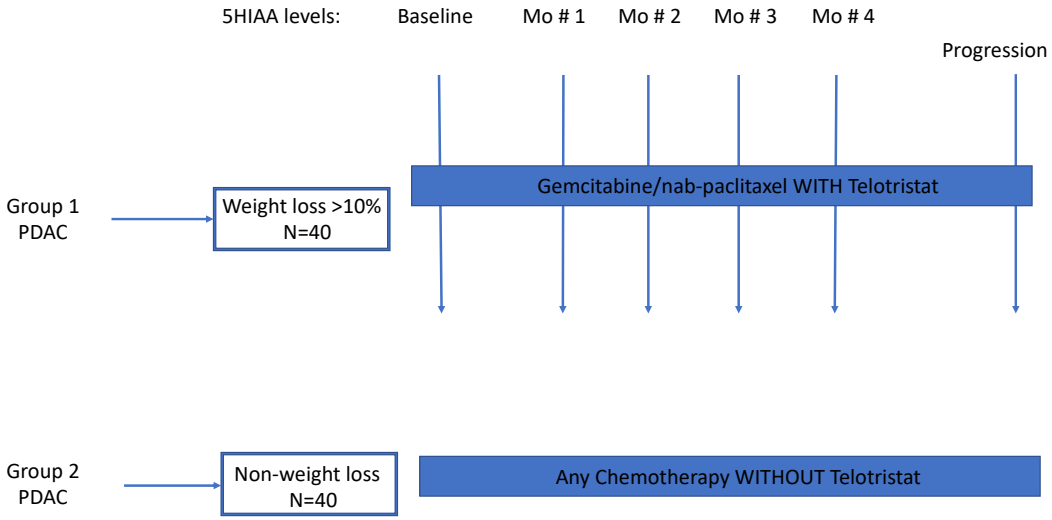
SCHEMA



1. BACKGROUND AND RATIONALE

1.1 Disease Background

The prognosis of pancreas adenocarcinoma (PCA) remains poor with little progress made in the last few decades with the exception of FOLFIRINOX (PRODIGE 4/ACCORD 11) [1] and gemcitabine/nab-Paclitaxel (MPACT trial) [2] treatments in 2011 and 2013, respectively. Current median overall survival (OS) for patients with advanced pancreatic cancer is between 8.5 and 11.1 months. Despite these advances, there is a continuous need to improve survival through the investigation of molecularly targeted agents.

Pancreas cancer (PDAC) patients have high prevalence of cachexia and anorexia with a median weight loss of 14% (10-20%) at the time of diagnosis to a progressive increase in weight loss to a median of around 25% in 6 months when on treatment. [3] Weight loss is often the presenting symptom of pancreas cancer. Weight loss is a multifactorial phenomenon including decreased calorie intake, systemic increase in pro-inflammatory markers, calorie loss through diarrhea (whether treatment induced or pancreas insufficiency), and abnormal metabolism. Cachexia and anorexia are associated with lower tolerance for chemotherapy, limiting the total dose that can be delivered, the number of symptomatic responses and the survival advantage associated with treatment. [4,5] Moreover, and added to the quality of life and treatment benefit, institution of early palliative care had shown improved survival benefit in lung cancer patients with a median survival benefit of 2.7 months [6] highlighting the importance of symptom control in the management of cancer.

In the gastrointestinal (GI) tract 5-HT contributes to motility, secretion, vasodilation, and sensation, and it also has both neuroprotective and pro-inflammatory actions in the gut. [7] The 5-hydroxytryptamine receptor 4 (5-HT_4R) is expressed in the colonic epithelium but little is known about its functions. Activation of colonic epithelial 5-HT_4R protects colons of mice from inflammation. 5-HT_4R activation maintains motility in healthy colons of mice and guinea pigs and reduces inflammation in colons of mice with colitis. [8] 5-HT_3 and 5-HT_4 receptors initiate one of the key colonic motility patterns, the colonic migrating motor complex, in rat by long distance contraction and rhythmic propulsive motor complex. Studies demonstrated that 5-HT is released in response to increased intraluminal pressure and that 5-HT is able to initiate the peristaltic reflex and propulsive motility. [9] 5-HT synthesis from L-tryptophan in enterochromaffin cells of the mucosa is mediated by the rate-limiting enzyme tryptophan hydroxylase 1 (TPH1); whereas, neuronal 5-HT synthesis is mediated by the rate-limiting enzyme tryptophan hydroxylase 2 (TPH2). Serotonin-containing neurons, although small in number (about 2% of all myenteric neurons) have broad, diverse projections which suggest a role in initiating and/or modulating gut motility. [10] Serotonin, regardless of its source, interacts with a variety of receptors present in the gut. Antagonists of the 5-HT_3 receptor have been used to treat diarrhea and abdominal pain, presumably through actions at 5-HT_3 receptors on intrinsic neurons that stimulate propulsive motility and extrinsic sensory neurons that signal pain and discomfort. [11]

Mice deficient in TPH1 (knocked down), the rate-limiting enzyme of serotonin synthesis in the GI tract, were healthy, despite a dramatic reduction in intestinal and blood serotonin [6]. Their serotonin deficiency was well tolerated in terms of GI function. In normal mice, telotristat ethyl was found to reduce serotonin levels throughout the GI tract. [12] The maximal effects observed with doses of telotristat ethyl was 150 mg/kg. No significant change in brain serotonin or 5-hydroxyindoleacetic acid (5-HIAA, a serotonin metabolite) was

observed. Telotristat ethyl is a novel, oral, small-molecule TPH inhibitor that has a high molecular weight and acidic moieties, which inhibit it from crossing the blood-brain barrier. Two early studies in patients with carcinoid syndrome suggested that telotristat ethyl reduced bowel movement frequency and decreased 5-HIAA without overt CNS adverse effects. [13,14]

Serotonin signaling has a role in carcinogenesis. Serotonin receptors are overexpressed on breast [15], prostate [16] and PDAC cell lines. [17] In preclinical trials, 5HT receptors were identified to play a role in carcinogenesis. The down-regulation of 5-HT_1B and 5-HT_1D receptors inhibits proliferation, clonogenicity and invasion of human PDAC cells through suppression of the β-1 integrin that decrease extracellular matrix proteins. In addition, the down-regulation of 5-HT1B and 5-HT_1D increases claudin 1 which decreases the transcriptional repressors needed for EMT resulting in the inhibition of invasion, migration and proliferation of the PDAC cells. [17] In a xenograft model, the increased serotonin signaling through the 5-HT_2B which contributes to the Warburg effect in pancreatic cancer cells and promotes growth of pancreatic tumors in mice. The knockdown of the 5-HT_2B receptor decreased the growth of the xenografted tumors. Following stimulation of the receptor, there was an increase activation of the PI3K- AKT-mTOR pathway leading to increased MYC and HIF1α expression. [18] This is suggesting an antitumor activity of Telotristat ethyl in PDAC.

1.2 Telotristat ethyl Clinical Experience

Telotristat ethyl (brand name Xermelo®) is a prodrug of telotristat ethyl, which is an inhibitor of tryptophan hydroxylase. The U.S. Food and Drug Administration approved Xermelo in combination with somatostatin analog (SSA) therapy for the treatment of adults with diarrhea associated with carcinoid syndrome that SSA therapy alone has inadequately controlled. [13] In a prospective, randomized study, patients with carcinoid tumor with symptoms of ≥4 bowel movements (BMs)/day despite stable-dose octreotide LAR depot therapy were enrolled in sequential, escalating, cohorts of four patients per cohort. In each cohort, one patient was randomly assigned to placebo and three patients to telotristat ethyl, at 150, 250, 350, or 500 mg three times a day (tid). In a subsequent cohort, one patient was assigned to placebo and six patients to telotristat ethyl 500 mg tid. Patients were assessed for safety, BM frequency (daily diary), 24 h urinary 5-hydroxyindoleacetic acid (u5-HIAA), and adequate relief of carcinoid gastrointestinal symptoms (using a weekly questionnaire). Twenty-three patients treated: 18 received telotristat ethyl and five received placebo. Adverse events were mild. Among evaluable telotristat ethyl-treated patients, 5/18 (28%) experienced a ≥30% reduction in BM frequency for ≥2 weeks, 9/16 (56%) experienced biochemical response (≥50% reduction or normalization in 24-h u5-HIAA) at week 2 or 4, and 10/18 (56%) reported adequate relief during at least 1 of the first 4 weeks of treatment. Similar activity was not observed in placebo-treated patients. Telotristat ethyl was well tolerated. Our observations suggest that telotristat ethyl has activity in controlling diarrhea associated with carcinoid syndrome.

In the phase III, international TELESTAR trial, 135 patients were randomized 1:1:1 to receive oral telotristat ethyl at 250 mg (n = 45) or 500 mg (n = 45) or placebo (n = 45) 3 times daily during a 12-week double-blind treatment period. Patients had well-differentiated metastatic neuroendocrine tumors and a documented history of carcinoid syndrome, were experiencing an average of at least 4 bowel movements per day and were receiving stable-dose somatostatin analog treatment for at least 3 months prior to enrollment. Patients remained on baseline stable-dose somatostatin analog therapy for the 12-week period. The primary

endpoint was change from baseline in the frequency of bowel movements.

Overall, 44% of patients were receiving above-label doses of stable-dose somatostatin analogs, and approximately 57% had urinary 5-HIAA levels above the upper limit of normal. Across treatment groups, the mean daily frequency of bowel movements ranged from 5.2 to 6.1 per day and mean urinary 5-HIAA levels ranged from 81.0 to 92.6 mg/24 h. At week 12, reductions in the mean frequency of bowel movements per day were –0.9 with placebo, –1.7 with telotristat ethyl at 250 mg, and –2.1 with telotristat ethyl at 500 mg. Compared with placebo, the estimated difference in bowel movement frequency averaged over 12 weeks was –0.81 per day with telotristat ethyl at 250 mg ($P < .001$) and –0.69 per day with telotristat ethyl at 500 mg ($P < .001$). Response—defined as a reduction in the frequency of bowel movements ≥ 30% from baseline for ≥ 50% of the 12-week period—was observed in 20% of the placebo group, 44% of the 250-mg telotristat ethyl group (odds ratio = 3.49, 95% confidence interval [CI] = 1.33–9.16), and 42% of the 500-mg telotristat ethyl group (odds ratio = 3.11, 95% CI = 1.20–8.10). Mean urinary 5-HIAA levels decreased by 40.1 mg/24 h ($P < .001$) and 57.7 mg/24 hours ($P < .001$) in the 250-mg and 500-mg telotristat ethyl groups vs a mean increase of 11.5 mg/24 h in the placebo group. In a post hoc analysis, a ≥ 30% reduction occurred in 78% and 87% vs 10% of patients, respectively. Nausea occurred in 31.1% of the 500-mg telotristat ethyl group, 13.3% of the 250-mg group, and 11.1% of the placebo group. Abdominal pain occurred in 22.2%, 11.1%, and 17.8%, respectively. Gamma-glutamyl transferase levels were elevated in 8.9%, 8.9%, and 0%, and alanine transaminase levels increased in 6.7%, 2.2%, and 0%. Depression-related adverse events occurred in 15.6%, 6.7%, and 6.7%. Treatment was discontinued due to adverse events in 6.7%, 6.7%, and 13.3%. The average diarrhea subscale scores on the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core 30 (QLQ-C30) improved by 19.2 points ($P = .039$) and 21.6 points ($P = .051$) on a 0-to-100 scale in the 250-mg and 500-mg telotristat ethyl groups vs 8.5 points in the placebo group. No significant differences among groups were observed in the nausea and vomiting subscale or in the global health status subscale. Some evidence of improved overall quality of life in responders vs. non-responders was reported in all groups.

In an open-label extension, 115 patients received telotristat ethyl at 500 mg. Mean treatment exposure was 26.7 weeks. Reduction in the frequency of bowel movements was consistent with that in the double-blind treatment period, and no new safety signals were observed. [19] The pre-specified subgroup analysis of the TELESTAR trial showed that the incidence of weight gain for patients on telotristat ethyl was dose related and greater than that on placebo. It was possibly related to reduce diarrhea severity and may be a relevant aspect of Telotristat ethyl efficacy among patients with functioning metastatic neuroendocrine tumors.

1.3 Rationale:

1. Serotonin may contribute to weight loss in pancreatic cancer patients. [21] Patients with clinically significant weight loss do not tolerate the chemotherapy treatment and have worse outcome. We hypothesize that stabilizing the weight by blocking serotonin synthesis will improve the overall performance status and enable these patients to tolerance of chemotherapy.
2. Serotonin affects GI motility, food absorption, and maybe related to tumor burden. We hypothesize that elevated baseline serotonin and its metabolite 5-HIAA will be

associated with weight loss in newly diagnosed patients with advanced pancreatic cancer (locally advanced unresectable, recurrent, and metastatic).

3. Serotonin as a ligand can promote PDAC cell growth and invasion and may contribute to resistance to therapy. We hypothesize that elevated levels of serotonin during treatment may contribute to resistance to therapy as well as ongoing weight loss.
4. Telotristat ethyl, a TPH inhibitor, has been shown in clinical trials of NET to inhibit serotonin production and impact bowel motility.

To test these hypotheses, we propose evaluating two cohorts of patients:

a. patients with weight loss at baseline – adding telotristat ethyl to chemotherapy will result in weight stabilization
b. Patients with no weight loss at baseline would have an increase in the 5-HIAA levels as they receive treatment leading to poor outcome.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective:

Aim # 1 - Group 1: Weight stability after 3 and 6 months of Telotristat ethyl treatment in patients who have significant weight loss (Documented to be more than or equal to 10%) prior to the start of treatment. This will be documented as % weight change at 3 and 6 months compared to baseline. These patients will be treated with gemcitabine/nab-paclitaxel combination chemotherapy.

Aim # 2 - Group 2: Evaluate the change in serum serotonin and 24-hr urine 5-HIAA in patients with locally advanced unresectable, recurrent or metastatic PDAC receiving chemotherapy. In this aim, we will include 40 patients who have stable weight or loss of <10%. These patients will be treated with chemotherapy (at the discretion of the investigator) and supportive care.

2.1.2. Secondary Objectives:

- Evaluate the impact of weight stabilization/gain on patients in Group 1 on performance status, quality of life (QOL), Mid Arm Circumference (MAC) and muscle mass on cross sectional imaging.
- Evaluate correlations between changes in serotonin/ 5HIAA levels on radiologic response, weight stability, Mid Arm Circumference (MAC), and muscle mass on cross sectional imaging
- Evaluate the relation of baseline serum serotonin and 24-hr urine 5-HIAA on weight loss in patients with advanced PDAC. For this aim, we will include baseline measurement from patients in Group 1 (N=40) and Group 2 (N=40)
- Safety and tolerability of telotristat ethyl with gemcitabine/nab-paclitaxel combination chemotherapy

- Evaluate response rate (RR) assessed per Response Evaluation Criteria In Solid Tumors (RECIST), progression free survival and overall survival in patients receiving telotristat ethyl (Group 1)

2.2. Endpoints

2.2.1. Primary Endpoint

- Weight stability will be documented as % weight change at 3 and 6 months or at time of progression compared to baseline. These patients will be treated with gemcitabine/nab-paclitaxel combination chemotherapy.
- Correlative descriptive markers of serum serotonin and 24-hr urine 5HIAA levels and chemotherapy effect on these levels

2.2.2. Secondary Endpoints

- Sarcopenia refers to the age-associated decreased in muscle mass and function. A single dimensional definition of sarcopenia using CT images that includes only assessment of the abdominal muscle mass as a measure of sarcopenia
- Mid Arm Circumference (**MAC**) will be measured in inches
- Quality of life testing through QOL questionnaire
- Blood serotonin levels will be compared in the 2 groups
- Toxicity evaluation will be assessed per CTCAE v4
- Response rate (RR) will be evaluated per RECIST 1.1
- Median overall survival (mos.) measured using the Kaplan-Meier method.
- Duration of response will be estimated from time of documentation of response to time of progression

3. ELIGIBILITY CRITERIA

Each of the criteria in the checklist that follows must be met in order for a subject to be considered eligible for this study.

Inclusion Criteria

GROUP 1 (Telotristat ethyl treatment group)

1- Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2- Weight loss of 10% or more

3- Age ≥ 18 years at the time of consent.

4- ECOG Performance Status of 0-2 within 14 days prior to registration.

5- Histologic or cytological diagnosis of recurrent or metastatic pancreas adenocarcinoma (PDAC) who present for first line chemotherapy treatment for metastatic disease.

6- Advanced stage pancreas cancer (recurrent/metastatic)

7- Measurable disease determined using guidelines of RECIST 1.1. Baseline tumor assessment should be performed using high resolution CT scans or MRI.

8- Prior systemic therapy (adjuvant or neoadjuvant setting are acceptable) if disease progressed or recurred within at least 3 months after treatment
9- Estimated life expectancy of > 12 weeks, as assessed by the site investigator.
10- If sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods) due to unknown risk of teratogenicity
11- Demonstrate adequate organ function as defined in Table 1 below; all screening labs to be obtained within 7 days prior to registration.
12- Prior radiation is allowed if happened more than 2 weeks of enrollment

Table 1: Organ Function Requirements

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Aspartate aminotransferase (AST)	≤ 3 × ULN or < 5 xULN in the setting of liver metastases
Alanine aminotransferase (ALT)	≤ 3 × ULN or < 5 xULN in the setting of liver metastases

Exclusion Criteria for Group 1 (Telotristat ethyl group)

1. Subjects with histology other than adenocarcinoma; Examples include: neuroendocrine tumors, acinar cell cancer, sarcoma or lymphoma of the pancreas
2. Ongoing or active infection
3. Symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia. Symptomatic heart failure (NYHA Class II-IV)
4. Acute or sub-acute intestinal obstruction
5. Ascites
6. Documented and/or symptomatic or known brain or leptomeningeal metastases.
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9. Breast-feeding or pregnant. Serum pregnancy test for women of child-bearing potential must be performed within 7 days prior to first dose of study treatment
10. Prior autologous or allogeneic organ or tissue transplantation.
11. Known allergy to any of the treatment components
12. Have any condition that does not permit compliance with the study schedule including psychological, geographical, or medical.
13. Not able to swallow. inability to take oral medications
14. Patients with chronic constipation

Inclusion Criteria-GROUP 2 (Correlative group- Non-Telotristat ethyl)

1- Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2- Stable weight or loss of < 10% by history
3- Age ≥ 18 years at the time of consent.
4- ECOG Performance Status of 0-2 within 14 days prior to registration.
5- Histologic or cytological diagnosis of locally advanced unresectable, recurrent/metastatic PDAC who present for first line chemotherapy treatment for metastatic disease.
6- Advanced stage PDAC (locally advanced unresectable/recurrent/metastatic)
7- Prior systemic therapy (adjuvant or neoadjuvant setting are acceptable) if disease progressed or recurred within at least 3 months after treatment
8- Estimated life expectancy of > 12 weeks, as assessed by the site investigator.
9- Prior radiation is allowed if happened more than 2 weeks of enrollment

Exclusion Criteria for Group 2 (Non-Telotristat ethyl group)

1. Subjects with histology other than adenocarcinoma; Examples include: neuroendocrine tumors, acinar cell cancer, sarcoma or lymphoma of the pancreas
2. Ongoing or active infection
3. Symptomatic congestive heart failure, unstable angina or arrhythmia. Symptomatic heart failure (NYHA Class II-IV)
4. Acute or sub-acute intestinal obstruction
5. Severely immune-compromised (other than being on steroids) including known HIV infection

4. SUBJECT REGISTRATION

All subjects must be registered through electronic data capture (EDC) system in Emory Oncore. A subject is considered registered when an "On Study" date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy.

5. TREATMENT PLAN

5.1. Treatment Regimen

- **Telotristat ethyl Treatment group:** Group 1 will receive gemcitabine/nab-paclitaxel combination therapy with Telotristat ethyl at a dose of 250 mg po TID and supportive care with a run-in phase trial design.

  A total of 40 patients will be enrolled with the aim to control weight loss by adding Telotristat ethyl.

  One cycle will be equal to 28 days.

- Group 2: Patients will receive chemotherapy (at the discretion of the investigator) and supportive care. This is the group that has no Telotristat ethyl drug intervention. We intend to collect serum serotonin and the 24 hr-urine for the 5HIAA at baseline and every cycle for the first 4 cycles to evaluate the effect of chemotherapy on the 5HIAA serum serotonin and urine levels and correlate the levels to response. We will correlate baseline levels to response/outcome and the change of levels while on treatment with response/outcome.

5.2. Pre-medications and Home Medications

Premedication will be given according to the institution standard prior to chemotherapy. No premedication needed for Telotristat ethyl.

5.3. Home Medications

At the discretion of the investigator. No specific medication will be given as a support to Telotristat ethyl

5.4. Drug Administration

Table 2. Drug Administration

Telotristat ethyl	Dose	Frequency of administration	Route of administration
	250 mg	Three times daily	po
DL-1	250 mg	Twice daily	po
DL-2	250 mg	Once daily	po

Telotristat ethyl of the 250 mg po tid will be held for Grade ≥ 3 (constipation (obstipation, constipation affecting activities of daily living, need of impaction) or for development of severe, persistent or worsening abdominal pain study drug related adverse events until recovery to Grade ≤ 1 and then resume at dose reduction of 250 mg po bid if the investigator evaluation relates toxicity to Telotristat ethyl. If a second Grade ≥ 3 related adverse events does not resolve within 2 weeks of the dose reduction, another dose reduction will be planned for 250 po once daily. If a third Grade ≥ 3 related adverse events does not resolve within 2 weeks of the dose reduction, the subject will be taken off the trial.

In case of grade 2 toxicity, continuation of the medication with a planned dose reduction to the lower dose level will be planned. In case toxicity remains at grade 2 as DL-1, then a plan to a DL-2 without interruption of treatment. The addition of stool softners and laxatives should be instituted from the first occurrence of any constipation grade.

Guidance for Constipation treatment:

Patients with a fecal impaction (a solid immobile bulk of stool in the rectum) should initially be disimpacted starting with manual fragmentation if necessary. After this is accomplished, an enema with mineral oil will help to soften the stool and provide lubrication.

If disimpaction is unsuccessful or only partially successful, a water-soluble soap enema will be advised. We suggest that sodium phosphate enemas be avoided in older adults.

Lactulose may be given after bowel cleansing to produce one stool at least every other day. The patient is instructed to use the bathroom after meals to take advantage of meal-stimulated increases in colonic motility. Bisacodyl or glycerine suppository is administered if there is no defecation after two days to prevent recurrence of fecal impaction. Alternatively, enemas may be administered.

Patient will be advised to drink lots of fluids, eat high fiber diet, and be active as possible. Bulk-forming laxatives include psyllium seed (eg, Metamucil), methylcellulose (eg, Citrucel), calcium polycarbophil (eg, FiberCon), and wheat dextrin (eg, Benefiber) is advised for all patients with any grade of constipation.

5.5. Missed Doses

All medications are given on Day 1. A missed dose implies delay of that cycle. Infusions may be given within 3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in subject's chart and case report forms. Telotristat ethyl should continue irrespective of the chemotherapy standard of care infusions. A missed dose of the Telotristat ethyl will not need to be made for the next day or double the dose. Patient should continue same daily dosing.

5.6. Supportive Care

Subjects should receive full supportive care in accordance with ASCO or equivalent guidelines on supportive care for solid tumors, if necessary. Supportive care measures may include but are not limited to anti-diarrheal agents, anti-emetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Subjects will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult with the principle investigator. Use of any supportive care therapy should be reported on the eCRFs.

5.6.1. Analgesic agents

The use of analgesic agents during the study is permitted at the discretion of the site investigator.

5.6.2. Antiemetic therapy
The use of antiemetic agents is permitted during this study and at the discretion of the investigator. However, it is recommended to follow the guidelines of the Multinational Association of Supportive Care in Cancer (MASCC) and ASCO.

5.6.3. Appetite Stimulants
The use of appetite stimulants is permitted at the discretion of the site investigator in Group 2 and will not be used in Group 1.

5.6.4. Blood Product Transfusions
Transfusions of red blood cells, platelets or other blood products are permitted at the site investigators discretion during the conduct of the study.

5.6.5. Contraception
Telotristat ethyl and chemotherapy may have adverse effects on a fetus in utero. Furthermore, it is not known if Telotristat ethyl has transient adverse effects on the composition of sperm. Subjects of childbearing potential should start using birth control from time of consent throughout the study period up to 90 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestin agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7. Treatment Compliance
Standard of care chemotherapy will be administered only at Emory sites approved for enrolling patients by the authorized study personnel. As a result, treatment compliance is ensured.

5.8. Concurrent Therapy
Additional concurrent chemotherapy or radiation therapy, biologic response modifiers, or other investigational agents may not be administered to subjects on this study. However, palliative radiation during the study is allowed if clinically indicated.

5.9. Concomitant Medications
Medications allowed:

- Medications required for supportive care during the study (See Section 5.6)

- Medications subject requires for treatment of previous comorbidities.

6. TOXICITY MONITORING AND DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events CTCAE v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

6.1. Dose Modifications for Telotristat ethyl

Telotristat ethyl of the 250 mg po tid will be held for Grade ≥ 3 study drug related adverse events until recovery to Grade ≤ 1 and then resume at dose reduction of 250 mg po bid if the investigator evaluation relates toxicity to Telotristat ethyl. If a second Grade ≥ 3 related adverse events does not resolve within 2 weeks of the dose reduction, another dose reduction will be planned for 250 po once daily. If a third Grade ≥ 3 related adverse events does not resolve within 2 weeks of the dose reduction, the subject will be taken off the trial.

Table 3. Modified dose of Telotristat ethyl

Dose level	Telotristat ethyl
Starting dose	250 mg po tid
Level -1 dose reduction	250 mg po bid
Level -2 dose reduction	250 po daily

6.2 Dose Modification for chemotherapy

The dose adjustment of chemotherapy agents will be according to the package inserts of each medication and according to what the investigator assessment of which medication to adjust. We will evaluate all the adverse events on study Group 1 (the Telotristat ethyl intervention group).

6.3 Protocol Therapy Discontinuation

For Group 1:

In addition to discontinuation from therapy related to toxicities, a subject will discontinue therapy with Telotristat ethyl and followed up per protocol under the following circumstances:

- The physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In case a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If protocol therapy is interrupted for ≥ 30 days.

For Group 2
The discontinuation of treatment will be left to the discretion of the investigator or the choice of the patient to discontinue the chemotherapy. If the therapy is discontinued, the blood and urine tests for 5HIAA will be discontinued.

6.4 Study Withdrawal

If a subject decides to withdraw from the study by revoking, all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the subject or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject's study withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. Stopping Rules

This is a run-in phase trial (For Group 1 only). Toxicity will be assessed within 28 days of enrollment on the combination treatment (Telotristat + gemcitabine/nab-paclitaxel). The dose limiting toxicity proposed as per table below (**Cumulative Distribution Function (CDF) Calculator for the Binomial Distribution)** for grade 3 constipation or perforation, the combination will be deemed not safe to proceed on the treatment and the study will halt accrual. This plan is for 10% of patients developing grade 3 constipation or perforation at any time point during accrual. We used the cumulative distribution function (CDF) to make sure there is at least 95% probability the true DLT rate is above 10% before stopping the trial for over-toxicity. Please note that if the trial stops at 10% of patients with DLT, it means that there is 50% chance that the true DLT rate is below 10%. But we aim to have at least 95% chance that the true DLT rate is above 10% before stopping the trial, therefore table allow for up to much higher percentage (>10%) of patients to incur a DLT before the study is stopped.

Total number of treated patients	Number of DLT to stop the trial for toxicity
3	≥1
4	≥2
5	≥2
6	≥2
7	≥2
8	≥2
9	≥3
10	≥3
11	≥3
12	≥3
13	≥3
14	≥3
15	≥4
16	≥4
17	≥4
18	≥4
19	≥4
20	≥4
21	≥5
22	≥5
23	≥5
24	≥5
25	≥5
26	≥5
27	≥5
28	≥6
29	≥6
30	≥6
31	≥6
32	≥6
33	≥6
34	≥6
35	≥7
36	≥7
37	≥7
38	≥7
39	≥7
40	≥7

9. STUDY CALENDAR & EVALUATIONS

CYCLE = 28 DAYS

Laboratory assessments and clinical procedures performed per SOC in the past 7 days are can be used as screening procedures.
Patients on arm 2 will follow standard of care visit schedule (as per institutional guidelines)

Examination	Screening	Cycle 1-2		Cycle 3–4		Cycle 5+		End of Treatment Visit (Cycle 6)	Follow up
	Within 7 days of registration	Day 1 (±7)	Day , 15[10] (±3)	Day 1 (±3)	Day 15[10] (±3)	Day 1	Day 15	30 days (± 7) after last dose of study drug	
REQUIRED ASSESSMENTS									
Demographics and Medical History/Height	X								
Physical Examination	X	X	X	X	X	X	X	X	
Vital Signs and ECOG PS[1]	X	X	X	X	X			X	
Comprehensive Metabolic Panel[2]	X	X	X	X	X			X	
CBC with Differential[3]	X	X	X	X	X			X	
Serotonin blood level[11]	X	X		X		X		X	
CA19-9[4]	X	X		X					
Pregnancy Test (Serum β-HCG)[5]	X								
Urine 5-HIAAs[6]	X	X		X		X		X	
AEs and Con Meds#	X	X	X	X	X			X	
Diagnosis Confirmation[7]	X								
Mid Arm Circumference (MAC) measurement	X	X		X		X		X	

Questionnaire QLQ-30	X	X		X				X	
DISEASE ASSESSMENT									
CT or MRI of Chest, Abdomen and Pelvis[8]	X			X				X	X[9]
TREATMENT									
Telotristat ethyl*		X	X	X	X	X	X		
Chemotherapy^		X	X	X	X	X	X		
FOLLOW-UP									
For progression, start of additional cancer treatment, and survival[9]									X[9]

1: Vital signs to include blood pressure, weight, height (screen only) and ECOG performance status.

2: CMP to include Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin, magnesium and uric acid

3: CBC to include Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets

4: CA19-9 at screening and every 2 cycles

5: Serum pregnancy test for women of child-bearing potential must be performed within 7 days prior to first dose of study treatment

6: 24 hr urine collection for 5-HIAA testing. This will occur at baseline and then monthly for 6 months (6 cycles)

7: Confirmation of diagnosis must be obtained during screening. A pathology report with staging information will be obtained from the institution that performed the diagnosis procedure.

8: Scans to be repeated every 8 weeks (± 7 days) until progression of disease. Pre-treatment scans to be performed within 28 days prior to registration. Abdominal muscle mass will be evaluated by a radiologist at every scan evaluation.

9: For subjects who discontinue study treatment without radiographically documented PD, the investigative sites will continue to evaluate tumor response every 8 weeks (± 7 days) by the same method used at baseline and throughout the study until time of disease progression, death or until study completion, except when not feasible in the opinion of the site investigator due to subject's clinical status. After the subject has documented PD, radiologic assessments are no longer required and the subject will be followed every 8 weeks (± 7 days) until the subject's death or study completion, whichever is earlier.

10: Each cycle is 28 days. Assessments will be done every 2 weeks

11: Serotonin blood levels. This will occur at baseline and then monthly for 6 months (6 cycles)

*Telotristat ethyl treatment is only for Group 1 of the study. It should be administered with food. Duration of treatment is until disease progression.

^ Treatment with chemotherapy will be gemcitabine/nab-paclitaxel combination for Group 1.
Group 2 chemotherapy will be decided by the investigator and should be either gemcitabine-based or 5fluropyrimidine-based therapy. Treatment schedule will differ depending on the chemotherapy regimen.

These are not needed for Group 2 of the study.

a. Screening

i. Within 28 Days Prior to Registration for Protocol Therapy:

-

The following should be collected before registration for protocol therapy:

- Prior to the subject being registered to the study, confirmation of diagnosis must be obtained via pathology report including staging information.
- Medical history and Height
- Physical examination
- Vitals Signs (including blood pressure), Weight [kg] and ECOG PS
- Laboratory Testing:
  - CBC with differential: Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets.
  - CMP: Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin
  - CA 19-9
  - Serum pregnancy test for women of child-bearing potential must be performed within 7 days prior to first dose of study treatment
  - Documented weight loss of > or = 10% as an estimate* NOT NEEDED FOR GROUP 2
- Radiological assessment (CT or MRI of chest, abdomen, and pelvis) with tumor measurements. Pre-treatment scans to be performed within 28 days prior to registration.
- Mid Arm Circumference (MAC)

ii. **On Treatment; Day 1 of each cycle**

Note: Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.

- Physical examination
- Vitals Signs (including blood pressure), Weight [kg] and ECOG PS
- Laboratory Testing:
  - CBC with differential: Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets.
  - CMP: Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin
  - CA 19-9 every 2 cycles
  - 24 hr- Urine for the 5HIAA levels
  - Questionnaire
- CT or MRI of chest, abdomen/pelvis after every 2 cycles of treatment
  Chemotherapy either gemcitabine/nab-paclitaxel combination chemotherapy or 5fluoropyrimidine-based depending on which group the patient is assigned to.

iii. **On Treatment; Day 15 of each cycle**

- Physical examination
- Vitals Signs (including blood pressure), Weight [kg] and ECOG PS
- Laboratory Testing:
  - CBC with differential: Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets.
  - CMP: Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin
- Chemotherapy either gemcitabine/nab-paclitaxel combination chemotherapy or 5fluoropyrimidine-based depending on which group the patient is assigned to.
- Patients will be evaluated every 2 weeks

iv. **Protocol therapy discontinuation:**

A subject will be discontinued from the protocol therapy under the following circumstances:

- Evidence of disease progression (per RECIST 1.1)
- Site physician determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy
- Subject exhibits unacceptable toxicity
- Female subject becomes pregnant
- Protocol therapy is interrupted for ≥ 30 days.

v. **Safety follow up visit 30 days (±7 days) after last dose of study treatment for cohort 1**

Subjects will be evaluated 30 days (± 7) after the last dose of study drug. Suggested testing includes:

- Physical examination
- Vitals Signs (including blood pressure), Weight [kg] and ECOG PS
- Laboratory Testing:
  - CBC with differential: Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume, mean cell hemoglobin concentration, leukocytes (WBC), neutrophils, lymphocytes, monocytes, basophils, platelets.
  - CMP: Sodium, potassium, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, calcium, random glucose, albumin
  - Mid Arm Circumference (MAC)* NOT NEEDED FOR GROUP 2
  - Serotonin blood levels and 24 hr urine 5HIAA levels
  - Questionnaire

vi. Follow-up

For subjects who discontinue study treatment without radiographically documented PD, the investigator will continue to evaluate tumor response every 8 weeks by the same method used at baseline and throughout the study until time of disease progression, death or until study

completion, except when not feasible in the opinion of the site investigator due to subject's clinical status.

After the subject has documented PD, radiologic assessments are no longer required and the subject will be followed up every 8 weeks (+/- 7 days) until the subject's death or study completion, whichever is earlier.

10. CRITERIA FOR DISEASE EVALUATION

a. Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [20]

i. Measurable disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

ii. Measurable lesions

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

iii. Non-measurable lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

iv. Malignant lymph nodes

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

v. Target lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with

the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

vi. **Non-target lesions**

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

b. Response Criteria

i. Evaluation of target lesions

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

ii. Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor-investigator.

iii. Evaluation of best overall response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
	Not evaluated	No	PR
PR	Non-CR/ Non-PD/ not evaluated	No	PR
SD	Non-CR/ Non-PD/ not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

c. Definitions for Response Evaluation – RECIST version 1.1

i. First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

ii. Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

iii. Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

iv. Duration of Overall Complete Response
The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

v. Objective response rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

vi. **Disease Control Rate:**
The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

vii. Time to Progression:
A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

viii. Progression Free Survival

A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

ix. Overall Survival

Overall survival is defined by the date of randomization to date of death from any cause.

x. Duration of response

Duration of response is defined by the date of first response to date of progression of the disease

11. DRUG INFORMATION

a. Telotristat ethyl (Xermelo)

i. Formulation and Storage:

Telotristat ethyl is a 250mg tablet: white to Off-white coated tablet with "T– E" debossed on one side and 250 debossed on the other side.

Telotristat ethyl dispensed in a monthly case for a total of 28 days of therapy. Each monthly case contains four weekly boxes. Each weekly box contains seven daily dose packs.

Telotristat ethyl is administered with food.
Duration of therapy is until disease progression.

ii. Storage

Stored at 25°C [77°F]; excursions limited to 15° C [59°F to 89°F).

b. Patient counseling information

Advise patient:

1. If the severe constipation or severe or persistent or worsening abdominal pain to discontinue Telotristat ethyl and contact healthcare provider
2. To take did not restart with food
3. If a dose is missed, take the next dose at the regular time. Do not take 2 doses at the same time to make up for the missed dose.

12. ADVERSE EVENTS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be utilized for AE reporting. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov

a. Definitions

i. Adverse Event

An Adverse Event (AE) is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE unless it is attributable to the study regimen by the site investigator.

ii. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence resulting in one or more of the following:

- Death- Death due to progression is not considered a SAE unless the site investigator feels the study drug contributed to disease progression.
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

iii. Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

iv. **Relatedness**

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is not related to the study drug(s)
Unlikely	Adverse Event is doubtfully related to the study drug(s)
Possible	Adverse Event may be related to the study drug(s)
Probable	Adverse Event is likely related to the study drug(s)
Definite	Adverse Event is clearly related to the study drug(s)

b. Reporting adverse events

i. Adverse Event (AE)

- AEs will be recorded from start of treatment until 30 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- AEs considered related to study drug(s) will be followed until resolution to Grade ≤ 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

ii. Serious Adverse Event (SAE)

10.2.2.1 Site Requirements for Reporting SAEs For Group 1 only (Telotristat ethyl treatment group)

- SAEs will be reported from start of treatment until 30 days after discontinuation of study drug(s).
- SAEs will be reported on the SAE Submission Form **within 24 hours** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The completed SAE Submission Form must be sent either electronically to coordinators on the trial. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements. The original copy of the SAE Submission Form and the email correspondence or fax confirmation sheet must be kept within the Trial Master File at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.2.1), sites must submit a follow-up SAE Submission Form within a reasonable timeframe

No SAE needed to be reported for Group 2 as treatment does not include Telotristat ethyl and the intervention is only checking blood and urine samples for serotonin and 5HIAA levels, respectively.

10.2.2.2 Sponsor-Investigator Responsibilities

Coordinator will send a SAE summary to the sponsor-investigator **within 24 hours** of receipt of SAE Submission Form. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

10.2.2.3 Requirements for Reporting to the Food and Drug Administration (FDA)

The PI will hold the IND. Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

13. STATISTICAL METHODS

a. General Considerations

This is a phase II, single institution, randomized, 2-arm trial evaluating the efficacy and safety of Telotristat ethyl combination with chemotherapy (Arm A) vs. standard of care chemotherapy (Arm B) in 80 subjects with advanced PCA, not amenable to curative treatment.

b. Study Design

i. Sample Size and Statistics

Aim # 1: Estimated weight loss in pancreatic cancer patients is 10 %. Weight stability is the primary end point. Percentage weight change will be calculated at month 3 and 6 relative to baseline, and a weight loss < 5% will be considered as clinical meaningful weight stability. A sample size of 40 achieves 81% power to detect a non-inferiority margin of -5% weight change from baseline using a one-sided Wilcoxon test. We assume the true weight change is 0% and follows normal distribution with standard deviation of 12%. The significance level (alpha) of the test is set at 0.05

Aim # 2: This is a descriptive end point to see if we can detect a difference of change in serotonin and 5HIAA levels compared to baseline (before chemotherapy treatment)

A sample size of 40 achieves 80% power to detect a mean of paired differences of 0.4 with an estimated standard deviation of differences of 1.0 and with a significance level (alpha) of 0.05000 using a one-sided paired t-test.

ii. Correlative markers

Aim # 1 and 2: We propose to check serum serotonin, albumin and 24-hr urine 5HIAA levels at baseline and every month when the patient is on chemotherapy and Telotristat ethyl treatment until disease progression.

Aim # 3: Evaluate QOLeffect on MAC and abdominal muscle

Aim # 4: Evaluate safety of the combination of Telotristat ethyl with gemcitabine/nab-paclitaxel combination treatment for Group 1.

Aim #5: Evaluate median progression free survival and overall survival in both groups

Aim # 6: Evaluate the response rates for patients on Group 1 and Group 2

c. Definition of Primary Endpoint

Weight stability over a period of 3 months while on trial.

d. Definitions of Secondary Endpoints

- Performance status will be assessed clinically
- Quality of life (QOL) will be assessed by the EORTC QLQ-30
- Mid Arm Circumference (MAC) and muscle mass on cross sectional imaging. This will be assessed with imaging guided measurements of the psoas and rectus abdominus muscle
- Evaluate correlations between changes in 5HIAA levels on radiologic response, weight stability, Mid Arm Circumference (MAC), and muscle mass on cross sectional imaging
- Evaluate the relation of baseline serum serotonin and 24-hr urine 5-HIAA on weight loss in patients with locally advanced unresectable, recurrent, metastatic PDAC. For this aim, we will include baseline measurement from patients in Group 1 (N=40) and Group 2 (N=40)
- Safety and tolerability of telotristat ethyl with gemcitabine/nab-paclitaxel combination chemotherapy assessed by the CTCAE v 4 to grade toxicities
- PFS is based upon the time of enrollment until progression or death. Disease is evaluated by CT/MRI scans of the organ(s) with the target lesion(s) based on RECIST 1.1 criteria.
- Overall survival is defined as the time of enrollment to time of death. Response is defined as a complete or partial response according to CT/MRI evaluations based on RECIST criteria.
- Duration of Response: Time from first response to time of progression evaluated by CT/MRI scans of the organ(s) with the target lesion(s) based on RECIST criteria.

e. Analysis Plan for Primary Objective

For the Aim # 1 of proving weight stability in the treatment arm, the patients in Group 1 will be treated with Telotristat ethyl and gemcitabine/nab-paclitaxel combination chemotherapy.

Their weight will be measured at baseline and after 3 and 6 months of telotristat ethyl treatment or at time of progression. The absolute weight change will be calculated by the weight after 3 months minus the baseline and the % weight will be the weight change at 3 and 6 months or time of disease progression compared to baseline. Weight stability is defined as weight change of less or equal to 5%. One sided Wilcoxon signed rank test will be used to test whether there is significant weight loss at 3 months after treatment compared to baseline, given a non-inferiority margin of -5%.

For the Aim # 2 of evaluating the change in serum serotonin and 24 hr urine 5-HIAA in the group 2 patients with locally advanced unresectable, recurrent, metastatic PDAC receiving chemotherapy, the change will be summarized as mean and standard deviation. Then one-sided paired t-test will be employed to test whether there is a significant change in serotonin and 5HIAA levels compared to baseline (before chemotherapy treatment). Finally, General linear model (GLM) will be used in the multivariate analysis to test whether the adjusted change is still significant after adjusting for other factors.

f. Analysis Plan for Secondary Objectives

Descriptive statistics will be first used to summarize weight stabilization/gain on patients, performance status, quality of life (QOL), Mid Arm Circumference (MAC) and muscle mass on cross sectional imaging. For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the sample size (n), mean, median, standard deviation, and coefficient of variation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. T-test, Chi-square test, General linear model will be further employed to test the impact of weight stabilization/gain on performance status, quality of life (QOL), Mid Arm Circumference (MAC) and muscle mass on cross sectional imaging.

Similarly, T-test, Chi-square test, General linear model will be further employed to evaluate correlations between changes in serotonin/ 5HIAA levels on radiologic response, weight stability, Mid Arm Circumference (MAC), and muscle mass on cross sectional imaging.

To evaluate the relation of baseline serotonin and its metabolite 5-HIAA on weight loss in patients with locally advanced unresectable, recurrent, and metastatic) pancreatic cancer, Pearson or Spearman correlation coefficient will be first used to measure their correlation. General linear model will be further used to estimate their adjusted relationship after adjusting for other factors.

RR will be estimated for each arm and reported along with exact 95% confidence intervals. A Fisher's exact test will be used to compare RR between the two arms. Toxicities will be described for each arm using frequency tables. Fisher's exact tests will be used compare toxicities between arms. The ITT populations will be used for secondary analyses related to OS and RR. The safety analysis dataset will be used for analyses related to toxicities.

For progression free survival, progression or death from any cause will be defined as the event. Patients will be censored at time of last follow-up. For overall survival, death from

any cause will be defined as the event. Patients will be censored at time of last follow-up. Overall survival (OS) and progression free survival (PFS) rates of two patient groups will be estimated with the Kaplan-Meier method and compared between different groups using the log-rank test, respectively. The PFS and OS of each patient group at specific time points, such as 6 moths, 1 year, 3 year, and 5 year, etc. will be also estimated alone with 95% CI. Cox proportional hazards models will be further used in the multivariable analyses to assess adjusted effect of treatment on the patients' OS and PFS after adjusting for other factors. Interaction terms between these factors will also be tested for statistical significance. The proportional hazards assumption will be evaluated graphically and analytically with regression diagnostics. Violations of the proportional hazards assumptions will be addressed by use of time-dependent covariates or extended Cox regression models.

g. Analysis Population

The intention-to-treat (ITT) population includes all subjects who meet the eligibility criteria and are registered onto the study irrespective of their compliance to the planned course of treatment. The intention-to-treat principle asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

The safety analysis dataset includes all subjects who are enrolled and receives a fraction of Telotristat ethyl (on either arm). Subjects will be analyzed for safety according to the treatment actually received.

h. Sample Size/Accrual/Study Duration

- Estimated weight loss in PDAC patients is 10 % within 3 months prior to diagnosis. Weight stability is the primary end point. Percentage weight change will be calculated at month 3 and 6 or time of progression relative to baseline, and a weight loss < 5% will be considered as clinical meaningful weight stability. A sample size of 40 achieves 81% power to detect a non-inferiority margin of -5% weight change from baseline using a one-sided Wilcoxon test. We assume the true weight change is 0% and follows normal distribution with standard deviation of 12%. The significance level (alpha) of the test is set at 0.05
- **Aim # 2-** This is a descriptive end point to see if we can detect a difference of change in serotonin and 5HIAA levels compared to baseline (before chemotherapy treatment)
- A sample size of 40 achieves 80% power to detect a mean of paired differences of 0.4 with an estimated standard deviation of differences of 1.0 and with a significance level (alpha) of 0.05 using a one-sided paired t-test.

The estimated enrollment period for this study is 12 months and the estimated study duration is 20 months.

i. Subject Characteristics

Baseline, demographic, and medical history information will be summarized for each arm. Demographic and baseline data will also be provided in by-subject data listings.

j. Concomitant Medications

Concomitant medication use will be summarized for each arm and will be included in by-subject data listings.

k. Disposition

A tabulation of subject disposition will be presented, including the number in each analysis population, the number who withdrew from treatment and the reasons for withdrawal, and the number who withdrew during the follow-up phase and the reasons for withdrawal.

14. TRIAL MANAGEMENT

a. Data and Safety Monitoring Plan

The study will be conducted in accord with the Winship Cancer Institute of Emory University's Data and Safety Monitoring Plan (DSMP).

In addition, data and safety activities include**:**

- Review all adverse events requiring expedited reporting as defined in the protocol
- Provide data summary reports to the sponsor-investigator on a monthly basis
- Submit data summary reports to the lead institution Data Safety Monitoring Committee for review as per their guidelines.

b. Winship Cancer Institute Data Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study which has been deemed Moderate Risk. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Since this study is Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review the following:

- Adverse event summary report
- Monitoring and/or audit results if applicable
- Summary of enrollment including number of subjects consented, enrolled, treated and active and discontinued
- Any regulatory compliance findings from all active sites
- Summary of investigational product accountability, handling, and dose delivery
- Summary of protocol compliance relative to tumor response evaluation
- Summary of data accuracy and timeliness of reporting

- Any site-specific concerns with elements above, with recommendation/documentation or corrective actions and re-monitoring as needed

The Winship Cancer Institute DSMC will review aggregate AE data on an annual basis. Documentation of DSMC reviews will be provided to sponsor-investigator. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work to address the DSMC's concerns.

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

c. Data Quality Oversight Activities

Remote validation of OnCore data will be completed on a continual basis throughout the life cycle of the study by study coordinators. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated. Corrections will be made by the study site personnel.

Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into OnCore. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents.

The trial site may also be subject to quality assurance audit by Lexicon. or its designee as well as inspection by appropriate regulatory agencies.

d. Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the

requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion.

15. DATA HANDLING AND RECORD KEEPING

a. Case Report Forms and Submission

This study will utilize electronic case report forms (eCRFs) in an electronic data capture system OnCore. OnCore will be compliant with Good Clinical Practices .

Generally, clinical data will be electronically captured in OnCore. If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in OnCore, according to study-specific objectives.

The completed dataset is the sole property of Emory University and will not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator.

b. Record Retention

To enable evaluations and/or audits from Health Authorities, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's clinic file. To comply with international regulations, the records should be retained by the site investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

c. Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

Subjects will be informed in writing that some organizations, including the sponsor-investigator and his/her research associates, Emory University, Lexicon, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects' identity will remain confidential.

d. Changes to the Protocol and Informed Consent

Study procedures will not be changed without the mutual agreement of the sponsor-investigator, Emory University IRB and Lexicon.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by the sponsor investigator and must be approved by Lexicon in addition to each site's IRB. Local requirements must be followed.

If a protocol amendment requires a change to the informed consent form, then the IRB must be notified. Approval of the revised informed consent form by the IRB is required before the revised form is used.

The site investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center.

Lexicon's willingness to supply study drug is predicated upon the review of the protocol. Sponsor-Investigator agrees to provide written notice Lexicon of any modifications to the protocol or informed consent.

16. ETHICS

a. Ethics Review

Each site must obtain approval of the final study protocol, including the final version of the informed consent form, from its IRB.

The site investigator must inform the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Sites will provide progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB as required by local regulations and guidelines.

b. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles which are consistent with ICH/Good Clinical Practice E6 as adopted by the FDA, and applicable regulatory requirements.

c. Informed Consent Process

The site investigator will ensure the subjects is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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