A Randomized, Double-blind, and Placebo Controlled Multicenter Phase II Trial Evaluating Anamorelin in the Prevention of Cancer Induced-Weight Loss and Anorexia in Patients Receiving First-line Treatment of Advanced Pancreatic Ductal Cancer

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Protocol Signature Page

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Protocol Synopsis

Study Title	A Randomized, Double-blind, and Placebo Controlled Multicenter Phase II Trial Evaluating Anamorelin in the Prevention of Cancer Induced-Weight Loss and Anorexia in Patients Receiving First-line Treatment of Advanced Pancreatic Ductal Cancer
Sponsor	Lahey Hospital & Medical Center
Countries and sites	Multi-center national study with sites in the US
Clinical Phase	Phase II
Indication	Treatment of malignancy-associated weight-loss and anorexia in patients with pancreatic adenocarcinoma
Study Design	Multicenter, double-blind**,** randomized, placebo-controlled study to evaluate the efficacy and safety of anamorelin HCl. 100 subjects with advanced pancreatic ductal adenocarcinoma and weight loss will be randomized 1:1 to anamorelin HCl 100 mg or placebo, taken orally once daily (QD) for a total of 25 weeks. Subjects will be instructed to take the study drug at least 1 hour before their first meal of the day.
Objectives	Primary: To demonstrate superiority of anamorelin HCl vs placebo on the gain in body weight at 13 weeks Secondary: To evaluate the improvement in anorexia symptoms and the safety and tolerability of anamorelin HCl at 13 weeks
Treatment groups	Group 1/Test group: Anamorelin HCl 100mg daily (Administered as 100mg tablets taken in fasting state) Group 2/Placebo group: Placebo daily (Administered as matching placebo tablets taken in fasting state)
Drug administration	Subjects will take 1 tablet on Day 1 (starting 3-5 days before the chemotherapy and daily thereafter until visit 10 (Week 25). Subjects will be supplied with study drug at visit 0 (Screening), and re-supplied at Visit 4 (Week 7), Visit 7 (Week 13). Tablets of study drug will be taken orally in mornings while fasting at least 1 hour before breakfast. Water is permitted prior to and with study drug.
Study duration	A total of 25 weeks to completion of study
Number of subjects	A total of 100 subjects with PDAC (advanced pancreatic ductal adenocarcinoma) will be randomized 1:1 to anamorelin or placebo. A total of 50 subjects in each group.
Target study population	Advanced pancreatic ductal adenocarcinoma-adult subjects with body mass index < 20 kg/m^2 or with involuntary weight loss of >5% within 6 months prior to screening
Inclusion Criteria	1. Signed written informed consent 2. Female or male ≥18 years of 3. Documented histologic or cytologic diagnosis of American Joint Committee on Cancer (AJCC) unresectable or metastatic pancreatic adenocarcinoma 4. Body mass index < 20 kg/m^2 or with involuntary weight loss >5% within 6 months prior to screening

	5. Ongoing problems with appetite/eating associated with the underlying cancer, as determined by having ≥ 4 points on the 5-item Anorexia Symptom[1] and ≤ 37 points on the 12-item FAACT A/CS 6. Subjects eligible to receive first line palliative chemotherapy 7. ECOG performance status 0 or 1 at screening 8. Acceptable hepatic function as defined by total bilirubin < 1.6 mg/dl unless associated with Gilbert syndrome, then total 9. Appropriate treatment with pancreatic enzyme replacement prior to trial initiation per treating physician's discretion. 10. Female subjects shall be: a) of non-childbearing potential b) of childbearing potential using reliable contraceptive measures and having a negative blood/urine pregnancy test at screening. 11. The patient must be willing and able to comply with the protocol tests and procedures All inclusion criteria will be checked at screening visit (Visit 0).
Exclusion Criteria	1. Patient with other forms of pancreatic cancer (e.g., neuroendocrine tumors) 2. Patient undergoing major surgery within 4 weeks of randomization or plans to undergo major surgery during study period 3. Women who are pregnant or breastfeeding 4. Patient with alternative cause of anorexia as determined by the investigator including: a) severe COPD requiring O2, b) severe heart failure (NYHA Class III- IV), c) second malignancy 5. Reversible causes of reduced food intake as determined by the investigator including but not limited to: severe mucositis (≥ NCI CTCAE version 5.0 grade 3), mechanical obstruction, severe nausea, vomiting, or diarrhea (≥ NCI CTCAE version 5.0 grade 3) 6. Patient unable to swallow pills 7. Patient with history of bariatric surgery, gastrectomy, or malabsorption disorder (gastritis, esophagitis) 8. Use of strong CYP3A4 inhibitors two weeks prior to study entry 9. Patient currently taking medications/compounds intended to increase appetite or decrease weight loss (e.g. testosterone, megestrol acetate, cannabis products, chronic corticosteroids, olanzapine for reason other than nausea control, mirtazapine (allowed if >4 weeks of use as therapy for depression) 10. Patient currently taking methylphenidate 11. Patient with current use of tube feeding or parenteral feeding

[1] The 5-item Anorexia Symptom Scale includes item C6, ACT3, ACT6, ACT7 and ACT10 in appendix 2.

	12. Patient with pleural effusion requiring thoracentesis, pericardial effusion requiring drainage, 2+ edema or ascites[2]. 13. Patient with uncontrolled or significant cardiovascular disease, including: a. History of myocardial infarction within the past 3 months b. A-V block of second or third degree (may be eligible if currently have a pacemaker) c. Unstable angina d. Congestive heart failure within the past 3 months, if defined as NYHA class III-IV e. Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, Wolff-Parkinson-White (WPW) syndrome, or torsade de pointes) f. Uncontrolled hypertension (blood pressure >150 mm Hg systolic and >95 mm Hg diastolic) g. Heart rate < 50 beats per minute on pre-entry electrocardiogram and patient is symptomatic 14. Patient with hyperglycemia that is not under management 15. Patient with uncontrolled pain. 16. Any condition, including the presence of laboratory abnormalities, which in the Investigator's opinion, places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study 17. Enrollment in a previous study with anamorelin HCl 18. Enrollment in another clinical trial during the time of this trial. All exclusion criteria will be checked at screening visit (Visit 0).
Efficacy Assessment	Primary Efficacy Endpoints: Change in body weight from baseline to week 13 Secondary Endpoints: 1. Absolute change in the FAACT 5 item Anorexia Symptom Score from baseline to week 13 as measured every 2 weeks 2. Safety and tolerability 3. Overall survival 4. Radiologic response to chemotherapy using CT/MRI by RECIST 1.1 criteria assessed at week 13 5. Weight gain at week 25 6. Change in FACIT-F: fatigue subscale, at baseline, week 13 and week 25
Exploratory Endpoints	1. Number of unplanned visits for symptom management as defined by unscheduled clinic visits, Emergency Room visits, or hospitalizations. 2. Percent of patients who require a change in either dose or treatment interval of intended chemotherapy.

[2] Grading system of International Ascites Club: grade 1: mild, detectable only by ultrasound; grade 2: moderate, moderate symmetrical distension of abdomen; grade 3: large or gross ascites, abdominal distention. (Reference: Hepatology 2003 Jul; 38 (1): 258

	3. Body Composition Analysis: ▪ Evaluate if baseline body composition measures predict tumor response or biochemical response (cancer antigen 19-9 (CA 19-9)). ▪ Evaluate if baseline body composition measures predict chemotherapy toxicities. ▪ Analyze if change in body composition is influenced by baseline demographic and disease-related characteristics.
Safety Assessment	The following safety assessments will be obtained during the Study: physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), CBC and Differential/CBC and ANC, comprehensive metabolic profile, tumor marker (CA19-9), urinalysis, adverse events (AEs) assessment, the overall survival on all subjects
Stratification	Treatment Regimens – FOLFIRNOX or Gemcitabine/Abraxane and ±10% weight loss prior to enrollment
Statistical Analysis of Efficacy	**Analysis Sets** Statistical analyses will be performed on the following subjects' sets: ● The Full Analysis Set (FAS): all randomized subjects ● The Modified Intent-to-Treat (MITT) includes all randomized subjects who take at least one dose of trial medication and for which post randomization data are collected. ● Per-Protocol (PP): subset of the randomized subjects who do not have major protocol violations ● Safety: all subjects who receive any study drug and will be summarized as per actual treatment **Primary Efficacy Endpoint Hypotheses and Tests** All summaries except safety and discontinuation of study treatment will be performed according to the Intent-to-Treat paradigm (as randomized)-unless otherwise requested The null hypothesis H_0 and the alternative H_1 are set up as: H_0: no treatment effect H_1: the primary endpoint has different means. **Sensitivity Analyses** Sensitivity analyses may be performed; some will be detailed and pre-specified in the Statistical Analysis Plan (SAP) **Supportive Analyses** Two analyses similar to the primary efficacy analysis will be conducted; one on the FAS population and another one on the PP. Primary efficacy endpoint will be presented for all the subgroups by the mean of a Forest Plot. **Secondary Efficacy Endpoints Hypotheses and Tests** If the primary endpoint shows benefit at the two-sided significance level of 5%, the secondary endpoints will be evaluated for providing

	significant benefit following a hierarchal approach, using change in anorexia score at Week 13 as the first secondary endpoint, the change in radiologic response per RECIST 1.1 criteria at Week 13 as the second secondary endpoint, change in patient in FACIT-F total score at Week 1 as the third secondary endpoint, and overall survival at week 25 as the final secondary endpoint. **Exploratory Efficacy Analysis** The exploratory efficacy analyses are aimed to explore the effect of the anamorelin on different endpoints and/or time points. All the quantitative exploratory endpoints analyses will use the same model described above for the secondary endpoints. Binary endpoints (responder analyses) will be analyzed using a CMH model to explore the correlation between the weight gain and the improvement on the patient-reported anorexia score, the Pearson's correlation coefficient will be estimated within each treatment group. Specific to the exploratory efficacy analyses as they relate to body composition, primary analysis of this exploratory aim will evaluate weight change from baseline to 13 weeks as a function of baseline body composition measures. Initially, all subjects will be pooled together to assess the statistical significance of baseline body composition measures (BBCMs) on weight change. Univariate linear models (regression or Analysis of Variance) will be used to identify individual prognostic factors among the BBCMs. Body composition measures identified to be individually significant prognostic factors ($p < 0.05$) will be included in a multivariable model. Backwards elimination ($p < 0.05$) will be utilized to identify BBCMs that are independently prognostic for weight change. Treatment group will then be added to a model including these independently prognostic BBCMs to assess the treatment group effect modification associated with these body composition measures. A similar modelling strategy will be used to assess the impact BBCMs on tumor response, biochemical response, and maximum severity great toxicities; however, logistic regression will be used to analyze these endpoints. Changes in BBCMs from baseline to Week 13 will be analyzed separately to assess the impact of demographic and disease-related characteristics on these changed in BBCMs. Body composition measures assessed by thresholds (Section H-10) will be analyzed using ordered-categorical logistic regression models and body composition measures assess quantitatively will be analyzed using linear models.
Statistical Analysis of Safety	All safety and tolerability data will be summarized descriptively according to the "As Treated" paradigm.

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A. ABSTRACT

A Randomized, Double-blind, and Placebo Controlled Multicenter Phase II Trial Evaluating Anamorelin in the Prevention of Cancer Induced-Weight Loss and Anorexia in Patients Receiving First-line Treatment of Advanced Pancreatic Cancer

B. SPECIFIC AIMS

1.0 Study Objectives

1. Primary Objective: To demonstrate anamorelin HCl superiority over placebo on gain in body weight.
2. Secondary Objectives: To evaluate improvement in anorexia, the safety and tolerability of Anamorelin HCl in subjects with pancreatic cancer.

2.0 Study Endpoint

- Primary efficacy endpoint
  The primary efficacy endpoint for this study is change of body weight from baseline to week 13
- Secondary efficacy endpoints
  Secondary efficacy endpoints will supplement our primary endpoints by further elucidating the degree and manner in which Anamorelin HCl improves outcomes. These will include:
  - Absolute change in the FAACT 5 item Anorexia Symptom Score from baseline score at week 13.
  - Safety and tolerability
  - Overall survival
  - Radiologic response to chemotherapy using CT/MRI by RECIST 1.1 criteria assessed at week 13
  - Weight gain at 25 weeks
  - Change in FACIT-F: fatigue subscale, at baseline, week 13 and week 25
- Exploratory endpoints
  - Number of unplanned visits for symptom management as defined by unscheduled clinic visits, Emergency Room visits, or hospitalizations.
  - Percent of patients who require a change in either dose or treatment interval of intended chemotherapy

3.0 Safety assessments

The following safety assessments will be performed: physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), CBC and Differential/CBC and ANC, comprehensive profile, tumor marker (CA 19-9), and urinalysis, adverse events (AEs) assessment, and the overall survival on all subjects. Please refer to section G Study Schedule of Assessments for timing/detail of assessments.

C. BACKGROUND AND SIGNIFICANCE

1.0 Background

Pancreatic cancer is the fifth leading cause of cancer deaths in the United States with rising numbers each year (1). Due to its aggressive nature, patients with pancreatic ductal adenocarcinoma (the most common subtype of pancreatic cancer) often present with advanced, non-resectable disease. Prognosis in these cases is poor with life expectancy 6-15 months with the use of standard of care therapy (2, 3). Weight loss and cachexia are commonly seen in PDAC with 90% of patients at risk of developing it during the course of their diagnosis and treatment (4). Weight loss, wasting, and cachexia have been shown to have a deleterious effect on response to treatment and confer a poor prognosis (5).

There remains a dearth of therapeutics available to combat the development of cachexia in patients with pancreatic adenocarcinoma. The current study aims to provide an option in the management of cancer-cachexia in an effort to improve prognosis and response to therapy in patients with pancreatic cancer.

The definition of cancer cachexia has changed significantly over time. Prior to consensus evaluation, definitions focused primarily on patient performance status and weight loss. Per current ASCO cancer cachexia guidelines-Journal of Clinical Oncology, cachexia is defined as the following:

- Weight loss >5% in preceding 6 months
- BMI <20 kg/m^2 and >2% weight loss
- Loss of muscle mass and >2% weight loss

Reduced food intake due to anorexia is a hallmark in the development of cachexia. While the etiology of underlying decreased intake is not well understood, there are some contributing factors that have been clearly demonstrated in previous studies. First, uncontrolled cancer symptoms including pain, change in taste, and nausea certainly contribute to decreased intake. Metabolic changes, particularly via elevated levels of inflammation in the setting of malignancy contribute to increased catabolism in patients with active cancer (6). Finally, physiologically, the homeostatic control of metabolism is modified due to alterations in the manner in which the hypothalamus controls appetite and food intake (7).

As previously noted, the presence of cachexia is an independent prognostic factor in patients with pancreatic cancer. Per the IMPACT study (8), the development of sarcopenia/muscle wasting during the course of treatment was a poor prognostic indicator irrespective of weight loss/gain. An additional study by Choi et al (9) demonstrated that sarcopenia was an independent predictor of negative outcome even in patients with early stage disease undergoing surgical intervention. Sarcopenia is a single aspect of cancer cachexia; anorexia alone also contributes to decreased quality of life as well as changes to treatment plans. Some patients' weight loss can be so severe that it results in treatment delays, dose reductions, or even treatment cessation which prevents these patients from achieving maximum benefit of their treatment plans (10). These findings have prompted a call to investigate strategies that will focus on aspects of cachexia separate from sarcopenia, including anorexia and weight loss that may impact patient outcomes (11).

Despite its prevalence and impact on quality of life and patient outcomes, there remains a dearth of options to address cancer cachexia. Prior groups have evaluated lifestyle and nutritional modifications with some success though compliance was difficult to achieve (12). There remains a lack of effective pharmacological interventions for the management of these highly morbid cancer sequelae.

Anamorelin HCl is an orally active selective ghrelin agonist that may serve to improve weight loss and anorexia via pharmacologic means. Ghrelin, a growth hormone secretagogue receptor, has been assessed as a potential target for the treatment of cachexia due to its ability to modulate systemic metabolism, regulate food intake, modify glucose metabolism, and protect against muscle atrophy (13). Initially it was unclear whether it would make a good target as its half-life is very short (approximately 15 minutes); however research on ghrelin and longer active ghrelin mimetics has been able to definitively demonstrate its ability to stimulate appetite, increase weight gain, and improve gi kinetics (14).

Anamorelin HCl has demonstrated high affinity for the ghrelin receptor with robust release of GH (growth hormone) in in vitro studies. In vivo animal studies with dog and rat subjects were able to increased appetite and weight in those subjects (15). A phase 3 study of patients with lung cancer demonstrated that the use of Anamorelin HCl resulted in increased lean body mass despite no increase in handgrip strength, highlighting its potential usefulness in the treatment of cancer related anorexia and weight loss (16).

2.0 Anamorelin: preclinical and clinical data

The pharmacological profile of anamorelin was studied in vitro and in vivo models. In particular anamorelin was screened for specificity against over 100 receptors, enzymes, transporters and ion channels. Moreover cardiovascular and other safety pharmacology studies were conducted. Studies were conducted to determine the absorption, distribution, metabolism and excretion of anamorelin in rats and mice. Toxicology studies were carried out primarily in rats and dogs, including single and repeated-dose studies for up to 26-week duration. Additional toxicology studies were performed to evaluate potential effects on fertility in rats, embryo-fetal development in rats and rabbits and assess the effects on tumor growth in mice. The most significant toxicity discovered during this phase of development of anamorelin HCl was the dose dependent prolongation of the cardiac QRS duration and PR interval caused by blockade of cardiac sodium ion channels. Overall these studies allowed to characterize the non-clinical profile of anamorelin as required to support its clinical development and marketing authorization applications in the future.

3.0 Anamorelin: Phase 1 Clinical Data

Anamorelin HCl has been studied in 15 Phase 1 studies in healthy volunteers of both genders including elderly with dosing up to 400 mg for a single-dose and up to 150 mg for multiple-doses. As noted above, Anamorelin HCl was found to increase levels of GH and caused significant appetite stimulation, body weight gain, and overall increased food intake. The threshold dose required for body weight gain is 50 mg once daily (QD). QD dosing in the fasting state is appropriate for anamorelin HCl; a split dose regimen offers no advantage over QD dosing and available data suggest that it may be less efficacious (17). No dose-limiting toxicity was observed up to 150 mg with multiple dosing; a single dose of 400 mg was determined to be the

maximum tolerated dose. A significant drug-drug interaction was observed with CYP3A4 perpetrators. CYP2D6 inhibition did not cause a clinically meaningful interaction with anamorelin HCl.

The most common adverse events observed from Phase 1 studies were fatigue, headache, dizziness, and nausea (18). Non-clinical events that were evaluated included transaminases, which was infrequent and QTc prolongation. While EKG abnormalities were initially of great concern, a dedicated study (HT- ANAM-113) revealed that anamorelin had no significant effect on cardiac electrical patterns.

4.0 Anamorelin: Phase II/III Clinical Data

The phase II program evaluating Anamorelin HCl evaluated its effect on individuals with numerous malignancies. 82 subjects were enrolled and randomized to anamorelin 50mg daily or placebo. Over 12 weeks, those in the anamorelin group showed significantly greater weight gain and increased lean body mass in comparison to the placebo group. Most noteworthy side effects included fatigue, dyspnea, and atrial fibrillation (19).

A second Phase II study evaluated the effect of differing doses of Anamorelin in subjects with advanced non-small cell lung cancer (20). 181 subjects were randomized to placebo, 50mg daily anamorelin, or 100mg daily anamorelin. There was a clear dose-dependent effect with those in the 100mg group on weight gain, performance status, and quality of life metrics.

A phase III program resulted in 2 separate studies, ROMANA-1 and ROMANA-2 both focused on subjects with advanced NSCLC. 484 subjects were enrolled at 93 separate sites. All were randomized 2:1 to anamorelin 100mg daily or placebo. Neither study resulted in a significant improvement in strength over the 12 weeks of study time. However, both studies demonstrated statistically significant improvement in lean body mass in the Anamorelin groups.

The primary purpose of the current study is to evaluate the effect of anamorelin on weight gain and anorexia symptoms in subjects with pancreatic ductal adenocarcinoma.

D. STUDY RATIONALE

1.0 Rationale for Study Population

This study will be performed in adult subjects with advanced pancreatic adenocarcinoma. This population was selected for investigation due to the prevalence of anorexia and weight loss present at the time of diagnosis. Additionally, baseline weight loss and anorexia over time carry prognostic implications including increased symptom burden and shortened survival.

To adequately assess our desired population, we plan to enroll those with BMI <20 and/or a 5% loss in body weight over the preceding 6 months, meeting the consensus criteria for cancer related weight loss and anorexia. These subjects are at higher risk for anorexia-related sequelae and would be the first group to benefit from an effective therapy. Additionally, as we are also assessing improvement in anorexia symptoms over time, our enrolled subjects must also demonstrate ongoing concerns with appetite and eating habits.

2.0 Rationale for Study Design

Anorexia and weight loss are common clinical sequelae of uncontrolled, metastatic cancer. These effects can impair physical function, reduce quality of life, impair tolerability of anticancer therapy, and reduce survival. Anorexia and weight loss are especially challenging problems in patients diagnosed with metastatic pancreatic cancer. With an annual incidence approaching 50,000 patients in the U. S. along, pancreatic cancer has an annual mortality of approximately 40,000 patients with most individuals succumbing to their disease within two years. Between 70-8-% of patients with metastatic pancreatic cancer experience cancer related anorexia and weight loss, which has been associated with reduced survival, increase risk of disease progression and impaired chemotherapy tolerance.

The study is a randomized, placebo controlled multicenter, Phase II trial to evaluate the efficacy and safety of anamorelin HCl. Approximately 100 patients with be enrolled in a 1:1 randomization to anamorelin HCl 100mg per day given concurrently with first-line chemotherapy compared to chemotherapy alone. Patients randomized to anamorelin HCl will take it daily for about 25 weeks starting 3-5 days prior to chemotherapy. Both body weight and appetite will be measured at enrollment as well as at the initiation of chemotherapy. Patients will be stratified by degree of weight loss in the six months prior to enrollment and choice of first-line chemotherapy.

3.0 Rationale for Selected Study Duration

The goal of the study was primarily to assess weight gain while on Anamorelin HCl in patients undergoing initial palliative treatment for pancreatic cancer. As such, the time frames for the study endpoints were aligned with the assessments for radiologic response to therapy implemented by the clinicians. Patients begin treatment with Anamorelin HCl 1 week before chemotherapy starts. Primary endpoint (weight change) along with a radiologic assessment of the primary cancer treatment will be assessed after 12 weeks of chemotherapy. As a means of assessing whether the effect of Anamorelin HCl was durable, its effectiveness in patients who continued on the study will be reassessed for an additional 12 weeks. Hence, a total of 25 weeks of assessment was defined for the study.

4.0 Rational for Selected Dose Range

In this study, 100 mg was selected as the dose of anamorelin HCl. This 100 mg dose had been evaluated in previously conducted Phase 3 studies (ROMANA-1 and ROMANA-2) in NSCLC subjects indicating that it was well tolerated and had a positive anabolic effect through both increased body weight and lean mass. An improvement in cancer anorexia symptoms/concerns in subjects with NSCLC was also observed. Follow up safety evaluation did not demonstrate increased adverse events with this dose. Thus, we feel that it provides the highest level of efficacy without increased risk of harmful side effects. As there is not a current safe and effective treatment for weight loss and anorexia in cancer patients, placebo treatment will be used in the control group in this study.

E. STUDY PLAN

1.0 Study Design

This is a multi-center, double-blind, placebo-controlled trial comparing Anamorelin HCl to placebo in subjects with advanced pancreatic adenocarcinoma with outcomes including safety and efficacy. 100 subjects will be randomized 1:1 to Anamorelin HCl 100mg daily or placebo for a total of 25 weeks.

The randomization will be stratified by the chemotherapy and ± 10%weight loss. Subjects will visit the site for evaluation every 2 weeks from week 1 to week 13 then every month from week 13 to week 25.

2.0 Study Duration

Each patient will remain on study for 25 weeks. Total number of visits will be 11. Subjects will be defined as completing the study when they have completed Visit 10 at week 25. The study will conclude when the final patient has completed his/her final visit.

3.0 Study population

Number of Subjects: A total of 100 subjects will be randomized 1:1 to Anamorelin HCl 100 mg or placebo. There will be 50 subjects in each group.

4.0 Eligibility

4.1 Inclusion Criteria:

- Signed written informed consent
- Female or male ≥18 years of
- Documented histologic or cytologic diagnosis of American Joint Committee on Cancer (AJCC) unresectable or metastatic pancreatic adenocarcinoma
- Body mass index < 20 kg/m^2 or with involuntary weight loss >5% within 6 months prior to screening
- Ongoing problems with appetite/eating associated with the underlying cancer as determined by [3] and ≤ 37 points on the 12-item FAACT A/CS
- Subjects eligible to receive first line palliative chemotherapy
- ECOG performance status 0 or 1 at screening
- Acceptable hepatic function as defined by total bilirubin < 1.6 mg/dl unless associated with Gilbert syndrome, then total bilirubin <2 x ULN, AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN or if hepatic metastases are present ≤5 x ULN
- Appropriate treatment with pancreatic enzyme replacement prior to trial initiation if indicated per treating physician's discretion
- Female subjects shall be:
  - of non-childbearing potential or
  - of childbearing potential using reliable contraceptive measures and having a negative blood/urine pregnancy test at screening
- The patient must be willing and able to comply with the protocol tests and procedures

4.2 Exclusion Criteria

[3] The 5-item Anorexia Symptom Scale includes item C6, ACT3, ACT6, ACT7 and ACT10 in appendix 2.

- Patient with other forms of pancreatic cancer (e.g. neuroendocrine tumors)
- Patient undergoing major surgery within 4 weeks of randomization or plans to undergo major surgery during study period.
- Women who are pregnant or breastfeeding
- Patient with alternative cause of anorexia as determined by the investigator including: a) severe COPD requiring O2, b) severe heart failure (NYHA Class III- IV), c) second malignancy
- Reversible causes of reduced food intake as determined by the investigator including but not limited to: severe mucositis (≥ NCI CTCAE version 5.0 grade 3), mechanical obstruction, severe nausea, vomiting, or diarrhea (≥ NCI CTCAE version 5.0 grade 3)
- Patient unable to swallow pills
- Patient with history of bariatric surgery, gastrectomy, or malabsorption disorder (gastritis, esophagitis)
- Use of strong CYP3A4 inhibitors two weeks prior to study entry
- Patient currently taking medications/compounds intended to increase appetite or decrease weight loss (e.g. testosterone, megestrol acetate, cannabis products, methylphenidate, chronic corticosteroids, olanzapine for reason other than nausea control, mirtazapine (allowed if >4 weeks of use as therapy for depression)
- Patient currently taking methylphenidate
- Patient with current use of tube feeding or parenteral feeding
- Patient with pleural effusion requiring thoracentesis, pericardial [4].
- Patient with uncontrolled or significant cardiovascular disease, including:
    a. History of myocardial infarction within the past 3 months
    b. A-V block of second or third degree (may be eligible if currently have a pacemaker)
    c. Unstable angina
    d. Congestive heart failure within the past 3 months, if defined as NYHA class III-IV
    e. Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, Wolff-Parkinson-White (WPW) syndrome, or torsade de pointes)
    f. Uncontrolled hypertension (blood pressure >150 mm Hg systolic and >95 mm Hg diastolic)
    g. Heart rate < 50 beats per minute on pre-entry electrocardiogram and patient is symptomatic
- Patient with hyperglycemia that is not under management
- Patient with uncontrolled pain.
- Any condition, including the presence of laboratory abnormalities, which in the Investigator's opinion, places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study
- Enrollment in a previous study with anamorelin HCl
- Enrollment or planned enrollment in another clinical trial during the time of this trial.

[4] Grading system of International Ascites Club: grade 1: mild, detectable only by ultrasound; grade 2: moderate, moderate symmetrical distension of abdomen; grade 3: large or gross ascites, abdominal distention. (Reference: Hepatology 2003 Jul; 38 (1): 258

All eligibility criteria will be checked at screening visit (Visit 0).

F. STUDY DRUG MANAGEMENT

1.0 Description of study treatments

- Anamorelin HCl, 100mg tablets to be taken daily while fasting at least 1 hour before first meal
- Placebo to be taken daily while fasting at least 1 hour before first meal

2.0 Treatment Groups

- Test group: 100mg Anamorelin HCl daily
- Control group: Placebo

3.0 Dose and Administration

Subjects will take 1 tablet on Day 1 (starting 3-5 days before the chemotherapy and then once daily thereafter until visit 10 (Week 25). Subjects will be supplied with study drug at visit 0 (Screening) and re-supplied at Visit 4 (Week 7) and Visit 7 (Week 13).
Used blister packs will be reviewed at each visit to determine drug compliance. Blister packs will be given back to the patient at visits that are not noted as drug resupply visits in section G.

The study drug tablets will be taken orally in mornings while fasting at least 1 hour before breakfast. Water is permitted prior to and with study drug.

4.0 Packaging

Packaging will be in the form of blister packs labelled with “Caution: New Drug-Limited by Federal Law to Investigational Use”. Study drug will be dispensed at the screening visit (Visit 0) and resupplied at visit 4 and visit 7. Patients will be dispensed one extra blister pack at the screening visit as an emergency supply in the event a scheduled visit is delayed out of window in the Study Scheduled of Assessments. Each pack will be labeled with an individual study drug kit number for assistance with identification and subject matching.

5.0 Storage

An exact inventory of all study drugs must be maintained at the investigational site. The study drug must be stored in a locked storage area under controlled environmental conditions appropriate for the product. Anamorelin HCl tablets and placebo tablets should be stored at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F). Site will notify the pharmacy at the Coordinating Center when/if a temperature excursion occurs.

6.0 Study Drug Distribution

The study drug kits will be shipped to participating clinical sites from the Coordinating Center Pharmacy. Study drug shipments to the investigational sites are triggered once the enrolled patient is randomized.

7.0 Accountability

Once the study drug kits are received at the study site, the pharmacist or designated responsible person will record receipt of study drug kits in dedicated paper forms. Adequate records of the receipt, dispensation and return of study drug kits must be maintained throughout the study.

Used study drug kits will undergo drug accountability performed by the Lahey Coordinating Center during the course of the study. Following drug accountability, used study drug kits are to be destroyed at the site until the end of the study. Used and unused study drug kits remaining at sites at the end of the study will be destroyed to the drug depots for destruction.

8.0 Randomization and Administration of Study Treatment

Randomization will be used to avoid bias in assigning treatments to subjects. Randomization tends to produce treatment groups in which the distributions of prognostic factors, known and unknown are similar; it also enhances the validity and the efficiency of statistical comparisons between the treatment groups. A 1:1 randomization with 2 stratification factors: Treatment Regimen – FOLFIRINOX or Gemcitabine/Abraxane and ±10% weight loss prior to enrollment will be employed. Block sizes, a detailed description of the stratification factors and the definitions of the strata, will be pre-specified in a separately crafted randomization plan.

Upon confirmation of subject eligibility (screening visit 0), the investigator at the site will request the randomization assignment for the patient from the study Coordinating Center. Each randomized patient is assigned a corresponding study drug kit number. The Coordinating Center will dispense and ship the assigned study drug kit to Principal Investigator at each participating site.

9.0 Blinding/Unblinding

This is a double-blind study. The blinding of the study drugs is guaranteed by the use of identical tablets for both placebo and the active drug.

Unblinding of the patient's treatment status should be avoided and generally should only be done in consultation with the Investigator; it should only be done in the event that unblinding may alter treatment decisions or otherwise be medically indicated.

Any unblinding of the study treatment will be performed as per industry standards and local practice.

10.0 Management of treatment overdosage

In case of overdose, conservative management of signs and symptoms is advised. No case of over-dosage has been reported with anamorelin to date. No antidote for anamorelin overdose is known. Supratherapeutic doses of up to 400 mg were administered in two phase 1 studies (one dose escalation study and one QT/QTc study). No clinically relevant ECG abnormalities were recorded for doses up to 300 mg.

11.0 Occupational safety

No testing has been performed on the ability to drive vehicles or operate machinery.

12.0 Prior and concomitant medications

Concomitant medications will be evaluated and noted from initial visit (day -14 to -7) and throughout the trial. If additional hydration or electrolyte replacement is necessary, it will be provided and documented in their medical record.

13.1 Use of corticosteroids

Systemic corticosteroids will be permitted for a maximum of 5 consecutive days for use in conjunction with chemotherapy or for sequelae/side effects from treatment. They may not be used as "appetite stimulants" at any time while on trial. Subjects requiring inhaled or topical corticosteroids may continue these.

13.2 Prohibited medications

Anamorelin HCl is metabolized via CYP3A4 and CYP2D6. However, Cytochrome P450 demonstrates moderate inhibitory effects against CYP3A4 and none against CYP2D6. Therefore the use of strong CYP3A4 inhibitors will be an exclusion criterion for this study. Drugs that strongly inhibit CYP3A4 including various antifungals and antibiotics will need to be avoided for the two weeks prior to initiation of the study as well as throughout its duration. If a patient is required to take a CYP3A4 inhibitor, then they will have to discontinue the study medication. Moderate or weak CYP3A4 inhibitors may be used; however should be avoided if possible. Additionally, any use of CYP3A4 inducers should be avoided as they may result in reduction of clinical effect. See appendix A for a list of CYP3A4 inhibitors and inducers.

Drugs that may prolong the PR or QRS interval durations are prohibited for the study duration. Subjects should not take any prescription medication or off-label products intended to increase appetite or treat unintentional weight loss during the study; these include: medical marijuana or dronabinol, testosterone or testosterone-like agents, olanzapine, megestrol, corticosteroids, or mirtazapine (though long term use of olanzapine or mirtazapine for psychiatric needs prior to study initiation may continue these therapies).

Subjects should not be on enteral or parenteral feeding throughout the duration of the clinical trial.

13.3 Concurrent APDC Treatment

All subjects enrolled in this study will be presenting for first line of therapy for metastatic disease. Per current NCCN guidelines standard of care therapy for metastatic pancreatic adenocarcinoma may include regimens with platinum and non-platinum based chemotherapy regimens.

Specific regimens that will be accepted include two regimens; 1. FOLFIRINOX and 2. Gemcitabine/Abraxane per investigator preference. Specific dosing and schedules for therapy will be at the discretion of the treating physician for each patient. The treating physician will calculate the anticipated dose for each patient and record any dose modifications made for individual patients while on trial.

Subjects will not be enrolled in any concomitant treatment clinical trials while participating in this study.

13.0 Rescue medications

Not applicable to this study.

14.0 Treatment compliance

Subjects will be instructed to bring all blister packs to each visit during the treatment period for assessment of compliance. Compliance will be summarized as proportions of subjects with compliance between 80% and 120% of the intended amount of drug

G. STUDY SCHEDULE OF ASSESSMENTS

Required for study	Pre-trial	Screening (visit 0)	Chemo teaching visit	Week 1 (visit 1)	Week 3 (visit 2)	Week 5 (visit 3)	Week 7 (visit 4)	Week 9 (visit 5)	Week 11 (visit 6)	Week 13 (visit 7)	Week 17 (visit 8)	Week 21 (visit 9)	Week 25 (visit 10)
Window (in days)		Within 14 days prior to randomization	within14 days of day 0	Day 0[12]	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)
Informed Consent		X											
Randomization[1]		X											
Chemotherapy Regimen selection	X												
Medical History		X											
Blood/urine Pregnancy Test (if applicable)		X											
Concomitant Medication		X		X	X	X	X	X	X	X	X	X	X
Physical Exam		X		X	X	X	X	X	X	X	X	X	X
Performance Status		X		X	X	X	X	X	X	X	X	X	X
Vital Signs[2]		X		X	X	X	X	X	X	X	X	X	X
ECG[3]		X			X								
Urinalysis[4]		X											
Weight		X		X	X	X	X	X	X	X	X	X	X
CBC and differential/ANC		X		X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Profile		X		X	X	X	X	X	X	X	X	X	X
Toxicity Notation[5]		X		X	X	X	X	X	X	X	X	X	X
CT or MRI for disease Assessment[6]		X								X			

Tumor Marker (CA 19-9)				X		X		X		X			
FAACT 5 questionnaire[7]		X		X	X	X	X	X	X	X	X	X	X
FACIT-F, fatigue subscale questionnaire[8]		X								X			X
Chemotherapy Initiation				X									
Drug initiation[9] (start drug)			X										
Drug resupply[13]							X			X			
Collection of unplanned visit data[10]													
Collection of change of chemo schedule or chemo dose[11]				X	X	X	X	X	X	X	X	X	X
Adverse Event Collection				X	X	X	X	X	X	X	X	X	X
Overall Survival				X	X	X	X	X	X	X	X	X	X

[1] randomization should happen at least 5 days prior to visit 1 to allow patient start taking the study drug 3-5 days before chemotherapy

[2] Vital signs include blood pressure, pulse rate and body temperature, body weight

[3] Further ECG assessments depend on treating physician's discretion

[4] Assessing abnormality per treating physician's discretion

[5] Toxicities are defined in section H1.0. Toxicities can be assessed remotely within 24 hours of the study visit if allowed per institutional policy

[6] CT or MRI for the screening visit should be within 4 weeks prior to randomization. CT or MRI for disease assessment by RECIST 1.1 criteria

[7] See appendix 2 for questionnaire. Questionnaire will be administrated prior to the chemotherapy on day of treatment. Questionnaire can be administrated remotely within 24 hours of the study visit if allowed per institutional policy.

[8] See appendix 3 for questionnaire. Questionnaire will be administrated prior to the chemotherapy on day of treatment. Questionnaire can be administrated remotely within 24 hours of the study visit if allowed per institutional policy.

[9] Drug should be initiated 3-5 days prior to the first chemo treatment.

[10] Unplanned visits will be collected at any time that event occurs.

[11] Change of chemotherapy schedule and/or dose will be collected at any time during treatment.

[12] Day 0 is the day that patients start their first chemotherapy treatment.

[13] Drug accountability should be documented and recorded at specified resupply visit (see pharmacy manual for a suggested log).

H. METHODS OF ASSESSMENT

1.0 Adverse Events

Adverse event recording will begin at the time the informed consent form is signed. Thereafter, AEs will be ascertained by direct report from the patient at each visit.

1.1 Definition of Adverse Events

Adverse Event (AE) as defined by the current ICH Guideline for Good Clinical Practice (21) is: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended symptom, clinical change, disease development, or lab/imaging finding associated with use of investigational drug or device irrespective of whether that finding is related to the drug or device. We would therefore consider any such occurrence to be an "AE" at any point after consent was signed whether the subject was exposed to the investigational drug or not.

The criterion used for grading the toxicities is the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

1.1.1 Expected Toxicities for FOLFIRINOX:

The most common grade 3-4 toxicities are: neutropenia, fatigue, vomiting, diarrhea, thrombocytopenia, sensory neuropathy, anemia, elevated alanine aminotransferase (ALT), thromboembolism and febrile neutropenia.

1.1.2 Expected Toxicities for Gemcitabine/Abraxane

The following toxicities are relatively common (≥20%) with Abraxane and gemcitabine combination treatment: neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting.

Severe hypersensitivity reactions with fatal outcome have been reported with nab-Paclitaxel treatment.

1.1.3 AEs Related to Anamorelin HCl Include the Following:

- Swelling of lower legs or hands,
- Fatigue,
- Diarrhea
- Nausea

Temporary decreases in systolic and diastolic blood pressure have been observed after taking first dose of the study drug.

Study related AEs can be attributed to the following conditions:

- Suspected adverse drug reactions
- Other medical challenges including: injury, accident, exacerbation of an underlying medical condition
- abnormal laboratory or physical exam findings

- Reactions from drug overdose, abuse, withdrawal, hypersensitivity, or toxicity.

Planned interventions or hospitalizations, including surgeries, scheduled prior to the informed consent but performed during the study (study procedures, chemotherapy cycles, etc.) should not be considered (serious) AEs.

1.2 Serious Adverse Event (SAE)
A serious adverse event is any event that suggests a significant hazard, contraindication, side effect, or precaution, whether or not it is considered to be associated with the study product. A SAE is an AE that meets any of the following criteria:

- Results in death. This includes any death that occurs during the conduct of a clinical study, including deaths that appear to be completely unrelated to the study drugs (e.g., car accident).
- Is life-threatening. This includes any AE during which the subject is, in the view of the Investigator, at immediate risk of death from the event as it occurs. This definition does not include events that may have caused death if they had occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Other medical events that based upon appropriate medical judgment are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

1.3 Unexpected Adverse Event
An Unexpected Adverse Event is any experience not previously reported (in nature, severity or incidence) in the current Investigator's Brochure for Anamorelin.

1.4 Pre-existing Condition
A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

2.0 Classification of Adverse Events
The Investigator will classify AEs based on their severity and relationship to investigational study drug. Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the investigational product (Anamorelin HCl).

3.0 Severity
The severity of an AE will be rated by the Investigator according to the descriptions and grading scales of the Common Terminology Criteria for Adverse Events (CTCAE version 5.0) (22) as summarized below:

Severity of AE according to CTC Grading Scale and related Guideline
Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*;
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**;
Grade 4 Life-threatening consequences; urgent intervention indicated;
Grade 5 Death related to AE.

(*) Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
(**) Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

4.0 Relationship to Investigational Study Drug

For this trial, an AE cause and effect relationship to the study drug will be classified by the Investigator and reported as follows.

Scale	Definition
Definitely related	The evidence is compelling that the study drug caused the adverse event. There is a clear temporal relationship of the event to the study drug; the event is consistent with a known pattern of drug (or drug class) effects; the event cannot be explained by concurrent disease or other drugs or chemicals; the event diminished upon cessation of study drug exposure or reduction in dose; the event worsened or recurred upon unintentional re-exposure to the study drug (intentional rechallenge for the purpose of assigning causality should not be performed).
Probably related	It is more likely that the event is due to the study drug than due to other etiologies, an alternative explanation is unlikely. There is a reasonable temporal relationship of the event to the study drug; the event may be consistent with a known pattern of drug (or drug class) effects; the drug seems more likely than other etiologies to cause the effect; the event diminished upon cessation of study drug exposure or reduction in dose.
Possibly related	It is equally likely that the event is due to the study drug as it is due to other etiologies. There is a reasonable temporal relationship of the event to the study drug; follows a known or expected response pattern of the suspected drug but could also have been easily produced by a number of other etiologies.
Unlikely related	It is more likely that the event is due to other etiologies than due to the study drug. The event could have been reasonably related to patient's underlying diseases or concomitant treatments and/or the temporal relationship is doubtful between the study drug and the suspected adverse event. It the temporal relationship of the event to the study drug is reasonable, but there are important confounding factors/reasonably

	convincing alternative explanations, causality is considered unlikely.
Not related	The study drug almost certainly (or certainly) did not cause the event. Sufficient information exists to indicate that the etiology is unrelated to the study drug, e.g. the event is more likely related to patient's underlying diseases or concomitant treatments and/or there is no temporal relationship between the study drug and the suspected adverse event, e.g. the event occurred before the study drug was administrated.
Not assessable	The data are insufficient or contradictory to make a meaningful

5.0 Reporting Adverse Events

AE reporting has to be in accordance with the ICH E6 (R2) Guidance on GCP. During the course of the study, all AEs, irrespective of the relatedness to the study drugs, must be recorded in detail in the source records.

During the course of an adverse event, severity and/or causality and/or seriousness may change. For CRF documentation each adverse event represents one entity from onset to resolution and the worst of the observed categories shall be attributed. When an event reoccurs after it has resolved, it should be handled as a new AE. However, when the same AE occurs intermittently without resolution, it can be recorded as one AE.

Adverse Events Associated with an Overdose

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the protocol. This includes accidental or intentional use of a drug in an amount higher than the dose being studied. An excess dose of study drug does not itself constitute an AE, though may contribute to one. All dose modifications (over or under) will be recorded and reported to the study Sponsor. If overdose results in AE, this will also be recorded and reported.

6.0 Reporting Serious Adverse Events

All serious adverse events (SAE) (including death and hospitalization) must be reported to Lahey Hospital & Medical Center Coordinating Center within one working day of the discovery of the event by telephone, email or fax. Applicable SAE forms should be completed in the electronic data capture system (EDC) within 5 days of discovery of the event and updated as new information becomes available. All deaths occurring on study must be reported to the Lahey Hospital & Medical Center Coordinating Center. These include deaths within 30 days of the end of study visits.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention.

7.0 Follow-up of Serious Adverse Events

SAEs will be followed by the Investigator until the subject is clinically stable, SAE has completely resolved, or patient is lost to follow up. This will be particularly important if the SAE has not been previously noted, or would have an effect on future monitoring for all sites. An updated SAE report should be completed in the EDC, including all missing information from the initial report, as appropriate. Any information from the initial report that is no longer accurate should be updated in the EDC as well.

8.0 Safety Monitoring Plan

All serious adverse events (SAE) (including death and hospitalization), premature withdrawal, and emergency treatment disclosures must be reported to the project program manager and Dr. Stuart at the Lahey Hospital & Medical Center Coordinating Center within one working day of site becoming aware of the event. Sites will notify Dr. Stuart and project program manager via email at (Keith.Stuart@lahey.org) (Essence.D.Maston@lahey.org). Please include Site Name, Patient study ID, SAE event term, grade and pertinent de-identified source documents. Decision on actions to be taken for the reported SAE will be made by Dr. Stuart and the participating site PI. Applicable SAE forms should be completed in the electronic data capture system (EDC) within 5 days of their discovery of the event and updated as new information becomes available.

9.0 Pregnancy Report

Patients who become pregnant while on study must immediately discontinue study treatment, and the pregnancy must be immediately reported to the Lahey Hospital & Medical Center Coordinating Center. Pregnancies occurring up to 30 days after taking the last dose of the study drug must also be reported to the project manager at the study Coordinating Center.

The Investigator should inform the patient of the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event of a pregnancy occurring in the partner of a male patient participating in the study, the participant should be requested to report the pregnancy to the investigator. The partner should also be informed of the risks of continuing with the pregnancy, the possible effects on the fetus by the participant or the treating physician. The pregnancy will be followed by the primary care physician or obstetrician. Even though pregnancy is not considered as SAE itself, pregnancy has to be reported within the timelines as defined for SAE.

10.0 Patient Discontinuation

A patient may withdraw from the study at any time and for any reason. It is intended that patients will be treated until investigator determined progressive disease or unacceptable toxicity. Some possible reasons for early discontinuation of study include, but are not limited to the following:

- Occurrence of any serious adverse event
- Occurrence of any serious adverse event, e.g. grade 3 or higher due to the chemotherapy treatment based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5

- Occurrence of severe hypersensitivity reaction to anamorelin
- QRS complex increases more than 15%
- Development of new tumor and/or progression of pre-existing tumor
- Abnormal liver function tests according to the recommendations of FDA Guidelines for drug-induced liver injury(https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation).
- Withdrawal of consent
- Investigator's decision
- Unable to receive treatments
- Lost to follow-up
- Pregnancy
- Protocol violation
- Termination of the study
- Other

If a patient withdraws from the trial, a complete final evaluation at the time of the patient's withdrawal should be made with an explanation of the reason for withdrawal. All patients who discontinue the trial as a result of an adverse event must be followed until resolution or stabilization of the adverse event. All patients who discontinue the trial will resume routine monitoring per their treating physician.

I. STATISTICS

All efficacy continuous variables will be analyzed via a linear model and the estimated treatment differences will be computed, adjusting for baseline values and the stratification factors. Binary variables (like responder analyses) will be analyzed using CMH models that account for the stratification factors.

For the primary endpoint: change from baseline in weight at week 13, the primary analysis may be augmented by using multiple imputations for missing data. Details of all analyses will be pre-specified in a statistical analysis plan (SAP) that is to be completed and signed prior to database lock. The planned enrolment of 50 subjects per treatment arm will give 95% power to detect a difference of 4kg assuming a two-sided significance level of 5%, and a standard deviation of 5.5kg.

The primary analysis will be executed for the Modified Intent-to-Treat dataset.

For all analyses, nominal p-values will be reported. If the primary endpoint shows benefit at the two-sided significance level of 5%, the secondary endpoints will be evaluated for providing significant benefit (2-sided 5%) following a hierarchal approach, using change in anorexia score at Week 25 as the first secondary endpoint, the change in radiologic response per RECIST 1.1 criteria at Week 13 as the second secondary endpoint, change in patient in FACIT-F total score at Week 13 as the third secondary endpoint, and overall survival at week 25 as the final secondary endpoint.

The expected accrual rate is 8 patients per month given that number of centers that are involved.

J. ETHICAL AND REGULATORY ASPECTS

1.0 Ethical Considerations

The study will be performed in accordance with the principles outlined in the Declaration of Helsinki (23) as amended by the World Medical Association in Fortaleza in 2013, and the ICH GCP guidelines as well as all local laws and regulations of the countries in which the study is conducted.

2.0 Laws and Regulations

This clinical study will be conducted in compliance with all national laws and regulations and national laws and regulations of the countries in which the trial is performed.

3.0 Patient's information sheet and informed consent form

All subjects invited to participate in the clinical trial are entitled to make their decision based on all current available information provided to them by the Investigator/designee. In addition, they will be given a document in English written in clear concise lay language for review and consideration. The document will previously have been approved by relevant independent Ethics Committee(s) (EC[s]/Institutional Review Boards [IRBs]) and may further be updated as new important information becomes available that may affect subject's willingness to participate or continue in the trial. This document will tell potentially eligible subjects about the nature of the study drug, its efficacy and safety profile, the route of administration, and the human experience available. It will also outline the steps of the protocol as they will apply to the individual, including the number of visits and types of procedures/assessments/measurements to be performed so that the individual has a clear picture of the risks, inconveniences and benefits that may accrue from the trial. The patient must be made aware that he/she may refuse to join the trial or may withdraw his/her consent at any time without prejudicing further medical care and that he/she is covered by the Sponsor's indemnity insurance in the event of a trial related injury. Contact details to report and discuss suspected trial related injuries will be provided. Subjects must also know that their personal medical records may be reviewed in confidence by the Sponsor's staff or representatives and by Regulatory Authorities and IRB/EC and that personal information will be collected and retained in a confidential database. Conditions for ensuring the anonymity of data and the security and confidentiality of the database should be explained. Consent will be given in writing after the patient has had adequate time to review the information and ask questions, if need be. Both the patient and the Investigator or responsible site staff member conducting the informed consent discussion will personally write the name, sign and date the consent form. Remote consent or electronic informed consent is allowed for the study and institutional policy has to be followed for such consent process.

4.0 Protocol amendments

Changes to the protocol may only be made by means of a written amendment, which has to be approved and signed by the authorized individuals of the Sponsor. Any amendment will require significant justifications that explain the need to modify the existing protocol. All amendments will first be reviewed by the Sponsor and will subsequently be submitted to the IRB for review

and approval. In the event of a change that is solely administrative (e.g., a new phone number or email address for a study personnel), IRB will be informed via email, but will not be required to approve the change.

5.0 Protocol deviations

The Investigator has to conduct the study in accordance with the approved current protocol and will not be allowed to make any changes unless immediate changes are necessary to protect the safety, rights, and welfare of the subjects. In order to obtain valid results, none of the investigators will alter the study conditions agreed upon and set out in this protocol. In the event of an isolated, unforeseen instance resulting in a protocol deviation, the investigator is to document this deviation and notify the Sponsor as soon as possible.

6.0 Project Management and Data Collection

Lahey Hospital & Medical Center (i.e., Sponsor) staff will accomplish all the tasks necessary for preparation and implementation of the project, including the drafting and refinement of the study protocol, development of the model consent document, assisting the PI in communications, developing project timelines, compiling required documents, preparing the detailed operations manual that outlines all the tasks required for study implementation at the sites, overseeing the distribution of documents, updating the protocol and operations manual as needed, updating regulatory files for the study overall, supervising the timely renewals of IRB approvals at the sites, and overseeing enrollment.

6.1 Records to Be Kept

Each participating site will maintain appropriate medical and research records related to this trial in compliance with regulatory and institutional guidelines for the protection of subject confidentiality.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to hospital records, clinical and office records, laboratory notes, subjects' HRQL data, radiology records, and treatment related records.

6.2 Data collection

Lahey Hospital & Medical Center in conjunction with Quartesian will design and distribute source worksheets and the electronic data capturing system that will maintain all data collected as part of the protocol. For the purposes of conducting the exploratory body composition analysis, a cloud-based data repository will be developed for the storage of CT/MRI imaging. Security features will include storage at a private secure facility, a published privacy policy, secure storage and transfers via secure socket layer (SSL) encryption, data back up, and password protected user access. The cloud-based storage will not house any identifiable PHI. The cloud-based storage and user access will be owned and governed by Lahey Hospital and Medical Center. Additionally, Levine Cancer Institute will receive clinical trial dataset in the form of a Limited Dataset for the purposes of conducting the exploratory body composition analysis.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. Collected study data must be entered into the study EDC within 5 days of the study visit. Source worksheets should be used as the primary data collection instrument for the study, when possible. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the EDC and all other required reports. Data reported in the EDC, that are derived from source documents, should be consistent with the source documents and any discrepancies should be explained. Any missing data must also be explained. An audit trail will be maintained by the EDC system.

Sites are required to provide the Sponsor with de-identified source documents supporting the data entered into the EDC system within 1 week of each completed visit. Source documents can be shared with the Sponsor via mailing, faxing, secure email and other external portal approved by study sites. Sites are required to provide the Sponsor with de-identified CT/MRI imaging within 2 weeks of each completed visit. CT/MRI imaging can be shared with the sponsor via upload to the secure, cloud-based data repository.

7.0 Study Monitoring and Quality Assurance

The site monitoring, regulatory review, adverse event reporting and quality assurance issues will be overseen by the Sponsor, Lahey Hospital & Medical Center. Each site will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. The Coordinating Center at Lahey Hospital & Medical Center will review and track Adverse Events, Serious Adverse Events, and Unanticipated Problems.

Centralized remote monitoring will be carried out by the Center at Lahey Hospital & Medical Center. Monitoring will occur through periodic review of submitted source data and data in the EDC system. A sample of enrolled patients may be randomly selected for a focused comprehensive audit of all data. Depending on enrollment progress, the goal will be to audit a 10% sample of enrolled patients from each site involved. The audit will be performed by comparing data submitted through the EDC against source documentation submitted by the site. If a greater than 10% error rate is discovered, an additional 10% sample will be selected to audit. Additional auditing may be initiated per the Sponsor's discretion.

8.0 Study Documentation and Records retention

The medical records of trial subjects should be retained in accordance with all applicable laws and in accordance with the policies of the participating institution (hospital or private entity), as well as with the clinical site agreement.
Investigators/institutions at each participating site will permit trial-related IRB review and regulatory inspection, including direct access to source data and documents. All the essential study documents should be retained at the sites for the period required by the Applicable Regulatory Requirements, or for a period of at least ten (10) years following the completion or discontinuation of the study, whichever is longer and in any case in accordance with FDA regulation 21 CFR 312.62(b) and (c)(24) and ICH-GCP guidelines. Should there be loss of documentation or move of documentation, the Sponsor should be promptly notified.

9.0 Confidentiality

The Investigator agrees to use such information only to accomplish the present study tasks and not to use it for any other purposes without the prior written consent by the Sponsor. Prior to the study start-up, each Institution/Investigator as well as each subcontractor to be involved in the study should sign a confidentiality agreement.

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APPENDIX 1: PROHIBITED MEDICATIONS

CYP3A4 Inhibitors
Strong CYP3A4 Inhibitors
ketoconazole clarithromycin itraconazole nefazodone telithromycin
Moderate CYP3A4 Inhibitors
aprepitant erythromycin fluconazole grapefruit juice verapamil diltiazem
Weak CYP3A4 Inhibitors
cimetidine

CYP3A4 Inducers
efavirenz nevirapine barbiturates carbamazepine enzalutamide glucocorticoids modafinil oxcarbazepine phenobarbital2 phenytoin2 pioglitazone rifabutin rifampin1 St. John's Wort troglitazone

This table is not all inclusive. For the most updated lists, please refer to the FDA website at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

APPENDIX 2: FAACT- FUNCTIONAL ASSESSMENT OF ANOREXIA/CACHEXIA TREATMENT QUESTIONNAIRE

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GP 1	I have a lack of energy……	0	1	2	3	4
GP 2	I have nausea……	0	1	2	3	4
GP 3	Because of my physical condition, I have trouble meeting the needs of my family……..	0	1	2	3	4
GP 4	I have pain ……..	0	1	2	3	4
GP 5	I am bothered by side effects of treatment……..	0	1	2	3	4
GP 6	I feel ill…….	0	1	2	3	4
GP 7	I am forced to spend time in bed……..	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GS 1	I feel close to my friends……..	0	1	2	3	4
GS 2	I get emotional support from my family……..	0	1	2	3	4
GS 3	I get support from my friends……..	0	1	2	3	4
GS 4	My family has accepted my illness……..	0	1	2	3	4
GS 5	I am satisfied with family communication about my illness…….	0	1	2	3	4
GS 6	I feel close to my partner (or the person who is my main support)…….	0	1	2	3	4

Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					
GS 7	I am satisfied with my sex life…….	0	1	2	3	4

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad…….	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness……..	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.	0	1	2	3	4
GE4	I feel nervous……..	0	1	2	3	4
GE5	I worry about dying……	0	1	2	3	4
GE6	I worry that my condition will get worse…….. .	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GF 1	I am able to work (include work at home)…….	0	1	2	3	4
GF 2	My work (include work at home) is fulfilling……	0	1	2	3	4
GF 3	I am able to enjoy life……	0	1	2	3	4
GF 4	I have accepted my illness…….	0	1	2	3	4

GF 5	I am sleeping well……..	0	1	2	3	4
GF 6	I am enjoying the things I usually do for fun…….	0	1	2	3	4
GF 7	I am content with the quality of my life right now	0	1	2	3	4

	ADDITIONAL CONCERNS	Not at all	A little bit	Some -what	Quite a bit	Very much
C6	I have a good appetite……..	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs.	0	1	2	3	4
ACT2	I am worried about my weight…….	0	1	2	3	4
ACT3	Most food tastes unpleasant to me……...	0	1	2	3	4
ACT4	I am concerned about how thin I look…….	0	1	2	3	4
ACT6	My interest in food drops as soon as I try to eat..	0	1	2	3	4
ACT7	I have difficulty eating rich or “heavy” foods…	0	1	2	3	4
ACT9	My family or friends are pressuring me to eat…	0	1	2	3	4
O2	I have been vomiting……..	0	1	2	3	4
ACT10	When I eat, I seem to get full quickly…….	0	1	2	3	4
ACT11	I have pain in my stomach area……...	0	1	2	3	4
ACT13	My general health is improving……...	0	1	2	3	4

APPENDIX 3: FACIT- FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY-FATIGUE SUBSCALE

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued……	0	1	2	3	4
HI12	I feel weak all over……	0	1	2	3	4
An1	I feel listless ("washed out")…….	0	1	2	3	4
An2	I feel tired……..	0	1	2	3	4
An3	I have trouble starting things because I am tired…..	0	1	2	3	4
An4	I have trouble finishing things because I am tired…	0	1	2	3	4
An5	I have energy…….	0	1	2	3	4
An7	I am able to do my usual activities……	0	1	2	3	4
An8	I need to sleep during the day……...	0	1	2	3	4
An12	I am too tired to eat……...	0	1	2	3	4
An14	I need help doing my usual activities……	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do……..	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4