EFFECTS OF ANAMORELIN ON CANCER-RELATED-FATIGUE IN PATIENTS WITH ADVANCED CANCER

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Study Sponsor: STRATEGIC ALLIANCE: HELSINN HEALTHCARE

A. STUDY OBJECTIVES

Primary Objective

- To evaluate changes in the Functional Assessment of Cancer Illness Therapy-Fatigue (FACIT-F) subscale score at Day 43± 3 days compared to baseline in patients with advanced cancer receiving oral **anamorelin** 100mg daily and standardized physical activity and nutritional counseling.

Secondary Objectives:

- To examine the effects of **anamorelin** and standardized physical activity and nutritional counseling on Health-related quality of life and patient reported outcomes as measured by The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), PROMIS-Fatigue, Hospital Anxiety Depression Scale (HADS), Edmonton Symptom Assessment Scale (ESAS), Functional Assessment of Cancer Therapy (FACT-G), and its Functional Assessment of Anorexia/Cachexia Treatment (FAACT) subscale in these patients.
- To examine the side effects and tolerability of **anamorelin** in these patients.

Exploratory Objectives:

- To explore the effects of anamorelin and standardized physical activity and nutritional counseling on muscle function (as measured by the 30 second chair stand test, 6 minute walk test, day time activity (accelerometer), body composition (as measured by INBODY), and Resting Energy Expenditure (measured by indirect calorimetry).
- To characterize the effects of anamorelin on potential inflammatory biomarkers of cancer-related fatigue (CRF) [C-Reactive Protein (CRP), monocyte IL-6&R, TNF-α&R, IL-10,IL-8, IL-1&RA; IGF-1]
- To explore the effects of anamorelin on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI).
- To determine the association between change in FACIT-F scores and changes in muscle function, day time activity, and body composition, in patients with advanced cancer receiving oral anamorelin 100mg daily and standardized physical activity and nutritional counseling.

We hypothesize that:

- **Anamorelin** and standardized physical activity and nutritional counseling are capable of significantly reducing the severity of cancer-related fatigue (FACIT-F subscale) between baseline and end of Week 6; additional beneficial effects on functional measures may also be observed (30 second chair stand test, 6 minute walk test, day time activity, body composition, and resting energy expenditure). We also hypothesize that in patients receiving anamorelin and standardized physical activity and nutritional counseling, improvement in fatigue scores (FACIT-F) will be significantly associated with improvements in muscle function, day time activity, and body composition.

B. BACKGROUND/ RATIONALE

Cancer related fatigue (CRF) is a frequent and serious consequence of cancer and cancer related treatment (Yennurajalingam, Frisbee-Hume et al. 2012, Yennurajalingam, Willey et al. 2012). As a result of improved cancer therapy, patients with advanced cancer are living longer, and due to advances in treatment for pain and nausea, clinicians are more frequently recognizing CRF as an important symptom that negatively affects quality of life (QOL). CRF in advanced cancer patients interferes with daily activity, has potentially devastating social and economic consequences, and affects the ability to receive palliative cancer therapy. Several strategies have been proposed for the management of CRF including physical activity, erythropoietin stimulating agents and psychostimulants (Berger, Abernethy et al. 2010). However, there are few pharmacological studies which show clinically relevant benefits. The most plausible reason is that these interventions have been unable to target mechanisms that cause CRF. Our group has shown that anti-inflammatory agents such as dexamethasone results in clinically significant improvement of fatigue; however, these agents are useful only for a short duration. However, due to their side-effect profile steroids can only be given for short duration (Yennurajalingam, Frisbee-Hume et al. 2013, Yennurajalingam and Bruera 2014). On the basis of previously described mechanisms and the results of studies, anamorelin has been shown to have potential beneficial effects on fatigue (including studies utilizing the FACIT-F subscale) in advanced lung cancer patients (Bruera, Strasser et al. 2003, Fearon, Barber et al. 2006, Currow and Abernethy 2014, Zhang and Garcia 2015, Takayama, Katakami et al. 2016, Temel, Abernethy et al. 2016). However, there were several limitations:

a) In the Phase 3 ROMANA studies with anamorelin, the co-primary endpoints were changes from baseline of lean body mass and handgrip strength; fatigue improvement was not a primary objective of the studies
b) Previous clinical studies with anamorelin did not include eligibility criteria around the presence or severity of fatigue as the primary outcome (the primary outcome was cachexia measures). Accordingly, the mean baseline values for the FACIT-Fatigue subscale in the Phase 3 ROMANA studies (~27-32 points on the FACIT-F subscale) were much higher than those observed in previous fatigue studies (Bruera, Yennurajalingam et al. 2013, Yennurajalingam, Frisbee-Hume et al. 2013).
c) The fatigue patient population was not well characterized in these studies (e.g. patients with depression/anxiety or anemia were not excluded; all types of fatigue patients, and C reactive protein levels, were included).

In contrast, in this current study, we plan to include patients with predominantly physical fatigue and high inflammation. The duration of efficacy and possible mechanisms of anamorelin on reduction of CRF have not been characterized as there was no attempt to understand the pathophysiologic characteristics of anamorelin using laboratory correlates in fatigued cancer patients. Based on all of the above information, the effects of the FACIT-F subscale on CRF and cytokine levels must be defined using validated tools and laboratory correlates in a well-defined population.

Conceptual Model: We adapted the Integrated Fatigue Model for this study to explain the complex multidimensional problem and multifactorial etiology of CRF and its treatments (Fig. 1) (Piper, Lindsey et al. 1987, Mock, St Ours et al. 2007). In this model, physical, behavioral, affective, and physiological/biochemical factors are the manifestation of multidimensional CRF in advanced cancer. Anamorelin uniquely affects outcomes including body composition and anorexia-related quality of life; some studies have also indicated that anamorelin may affect the inflammation that has been shown to mediate CRF (Butt, Rosenbloom et al. 2008, McNeely and Courneya 2010). By targeting the known mechanisms of CRF that are more likely to be affected by anamorelin based on previous research, we anticipate significant improvement of CRF.

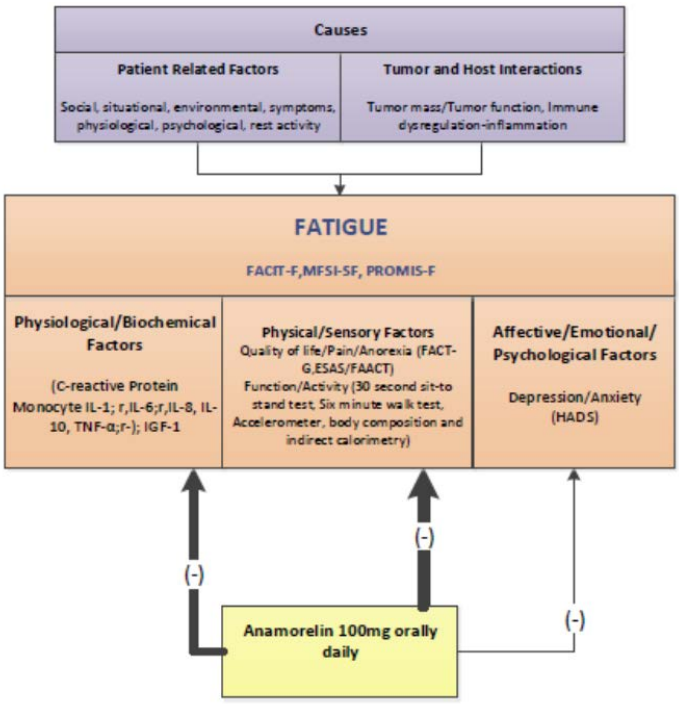


Figure 1. Conceptual Model (adaptation of the integrated Fatigue Model) shows various causative factors of multidimensional fatigue and potential targets of anamorelin

Significance: CRF is more severe and debilitating in patients with advanced cancer than in patients with early cancer or in cancer survivors (Butt, Rosenbloom et al. 2008, Hagelin, Wengstrom et al. 2009, Berger, Abernethy et al. 2010). However, because of the limited number of clinical trials studying CRF in advanced cancer as a primary outcome, few standard treatment options currently exist (Yennurajalingam and Bruera 2007, Butt, Rosenbloom et al. 2008, Minton, Richardson et al. 2010, Minton, Richardson et al. 2011) Recently, the National Institutes of Health State-of-the-Science Conference issued a statement that calls for the development of new treatments for CRF (Panel 2003, Butt, Rosenbloom et al. 2008, Barsevick, Irwin et al. 2013). The results of the proposed project would help us prescribe a safe and effective intervention, treatments that have shown preliminary evidence of efficacy in improving CRF in cancer patients (Butt, Rosenbloom et al. 2008). As preliminary studies suggest(Bruera, Roca et al. 1985, Cramp and Byron-Daniel 2012, Yennurajalingam, Frisbee-Hume et al. 2012, Yennurajalingam, Frisbee-Hume et al. 2013), we anticipate that treatment with **anamorelin** will result in a more robust and clinically effective improvement of CRF (Reddy, Bruera et al. 2007). This would, in turn, facilitate patients' decision to continue cancer therapy, since therapies would be better tolerated and thus more effective in controlling disease. Other important benefits of this study include providing important data on the role of **anamorelin** in other QOL measures such as MFSI-SF, PROMIS-Fatigue, HADS, ESAS, FACT-G, and the role of **anamorelin** on objective measures of physical activity, muscle function, potential inflammatory biomarkers of CRF, and anamorelin pharmacodynamics marker: IGF -1.

C. PRELIMINARY STUDIES

Pharmacologic Treatment of Fatigue: Our team's studies in patients with advanced cancer allowed us to establish the high frequency, severity and multidimensional nature of fatigue (Bruera, Roca et al. 1985, Bruera, Ernst et al. 1998, Bruera, Neumann et al. 1999, Bruera, Driver et al. 2003, Bruera, Valero et al. 2006, Bruera, El Osta et al. 2007, Yennurajalingam, Palmer et al. 2011, Yennurajalingam, Urbauer et al. 2011, Yennurajalingam, Frisbee-Hume et al. 2012, Yennurajalingam, Frisbee-Hume et al. 2013).We conducted studies using various assessment methods for fatigue and were able to characterize fatigue in this patient population (Bruera, Kuehn et al. 1991, Bruera, Michaud et al. 2001, Yennurajalingam, Palmer et al. 2008, Yennurajalingam, Urbauer et al. 2011, Yennu, Urbauer et al. 2012). In a preliminary study of 31 advanced cancer patients, we found that

methylprednisolone (MP) 32mg/day significantly improved CRF ($p<0.01$) compared with placebo with no significant differences in side-effects between groups (Bruera, Roca et al. 1985). This study was unable to detect sustained responses to Day 33 perhaps due to low doses, type of the steroid, and lack of validated tools. In a recently published (Yennurajalingam, Frisbee-Hume et al. 2013) randomized-controlled study of 84 patients with advanced cancer, oral dexamethasone (DM) at 8 mg/day for 14 days was found to be effective in alleviating CRF compared with placebo. The mean improvement in the FACIT-F subscale at Day 15 was significantly higher in the DM group than in the placebo (9 [10.3] vs. 3.1 [9.59], P=0.008)(Yennurajalingam, Frisbee-Hume et al. 2013).

Prior physical activity studies by our team:
Prior studies led by Dr. Basen-Engquist tested interventions in patients with highly symptomatic prostate cancer (TPRB-98-103-01-PBP) (Carmack Taylor, Demoor et al. 2006), advanced colorectal cancer, and breast cancer (CA89519) (Basen-Engquist, Taylor et al. 2006). The breast cancer study showed improved 6-minute walk performance and QOL (Basen-Engquist, Taylor et al. 2006). In an R01-funded study of physical activity in endometrial cancer survivors (Basen-Engquist, Scruggs et al. 2009), the intervention was completed by a high percentage of patients and was well received among the participants. The same methods will be used in the proposed study. In the next few months, a 154-person trial comparing a home-based physical activity intervention to a relaxation intervention for improving physical functioning and managing symptoms in advanced colorectal cancer patients (R21 CA137333) will be completed. To date only 5 patients in the physical activity arm have experienced adverse events (AE; 9 AE total, 1 definitely attributable to physical activity, 8 possibly attributable. All AE were grade 1 (5) or grade 2 (4). None of the AEs were due to falls.

A recently completed study in highly symptomatic prostate cancer patients, NCT01410942, conducted by the same team as that in the proposed study (PI: Yennu; Co-I: Basen-Engquist), used the same standardized exercise regimen in combination with study drug. Table 1 shows the adherence rates and safety data of the first 12 patients enrolled (blinded). The enrolled patients in this study had no difficulty in completing all the assessments. Based on the preliminary data presented, we conclude that this proposed physical activity would be feasible and safe.

Table 1. Preliminary adherence rates and safety data of first 12 patients (blinded)

Preliminary data of adherence and safety of exercise and attention control exercise patients on an ongoing multimodal fatigue study (NCT01410942)							
Pt. no	% calls completed	Goals met week 2	Goals met week 3	Goals met week 4	Goals met week 5	Goals met week 6	Exercise side effects
1	100%	yes	yes	yes	yes	yes	none
2	100%	yes	yes	no/foot pain	yes	yes	none
3	100%	no/back pain	no/back pain	no/epidural back	no	yes	none from exercise
4	100%	yes	yes	no/fatigue	yes	yes	none
5	100%	yes	no/no time	no/no reason	yes	yes	none
6	100%	no/soreness	no/no time	no/fatigue	no	no/fatigue	soreness
7	40%	no	no answer	no answer	no answer	yes	none
8	100%	no	no/no time	yes	no	no/shoulder pain	yes/shoulder pain
9	80%	no/fatigue	no	no/no time	no answer	no	none
10	60%	yes	no/fatigue	no/no time	w/d	w/d	none
11	withdrew						
12	80%	no/fatigue	yes	no/fatigue	no answer	yes	fatigue

Prior Inflammatory cytokine and CRF studies by our team:
Prior studies (Reuben, Lee et al. 2000, Wang, Shi et al. 2008, Foster, Lu et al. 2012, Yennurajalingam, Willey et al. 2012) by our group showed wide variability in serum cytokine levels in patients with advanced cancer and hence the need to assess cytokines levels in LPS activated monocytes. Physical activity results in modulation of TNF-α, IL-1β, and IL-6,(Ostrowski, Rohde et al. 1998) interleukin-1 receptor antagonist (IL-1RA), TNF-receptors (TNF-R), and IL-10 levels.(Ostrowski, Rohde et al. 1999) Since most of these factors are produced by activated

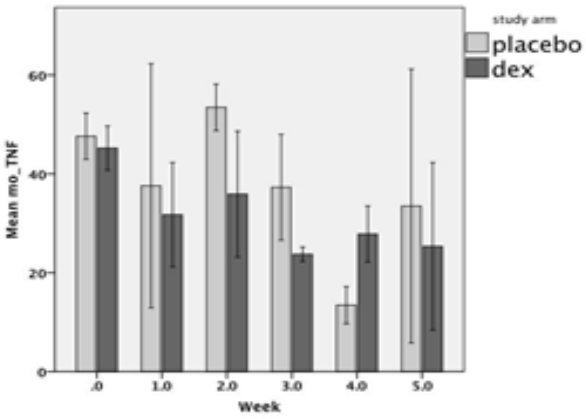


Figure 2. Change in TNF-α production by LPS-activated monocytes from dexamethasone-treated patients and placebo-treated patients in double-blind phase (Days 8 and 15) and in dexamethasone-only open-label phase (Days 29 and 35).

monocytes/macrophages, we propose to assess the synthesis of these factors by resting (unstimulated) as well as LPS-activated peripheral blood monocytes isolated from patients before and after study treatment.

Figure 2 shows the synthesis of TNF-α by LPS-activated monocytes isolated from patients at baseline (D0) and at weeks 1- 5 after treatment with dexamethasone (DM). In patients treated with 8 mg DM daily (dark histograms), the percentage of LPS-activated monocytes that synthesized TNF-α decreased, whereas in patients receiving placebo (light histograms) for the first 2 weeks there was no change in the percentage of LPS-activated monocytes that synthesized TNF-α from D0 until week 2. Thereafter, when placebo patients (light histograms) switched to open-label DM, there was a decrease in the percentage of LPS-activated monocytes that synthesized TNF-α. Hence analyses of the levels of cytokines from induced monocytes would help to determine their association with change in CRF and treatment, as shown in our previous studies (Naing, Reuben et al. 2011, Foster, Lu et al. 2012, Yennurajalingam, Frisbee-Hume et al. 2012).

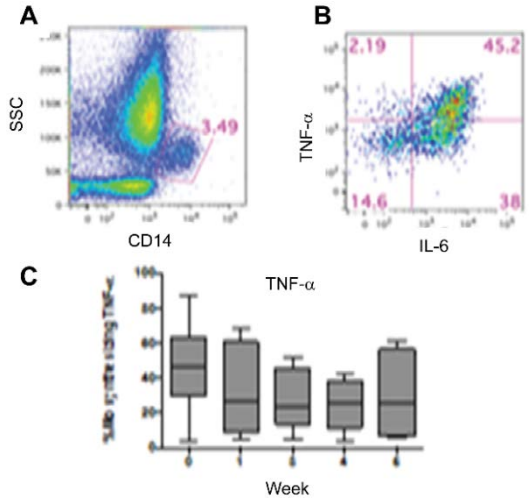


Figure 3. Monocyte Phenotype and LPS-induced cytokine synthesis. (A) Monocytes are enumerated in whole blood as $CD14^{+}SSC^{mid}$ cells. (B) After a 4 hour incubation with LPS, the percentage of cells synthesizing cytokines can be enumerated. (C) TNF-α synthesis by monocytes decreases in patients treated with 8 mg dexamethasone daily.

Summary of Anamorelin Efficacy in Clinical Trials:

Anamorelin HCl is under development for the treatment of cancer anorexia, cachexia or unintended weight loss in patients with NSCLC, a critical unmet medical need characterized by poor appetite, loss of lean (muscle) mass, and strongly correlated with increased mortality. Various Phase 2a and Phase 3 studies conducted by Helsinn in patients with cancer anorexia-cachexia have demonstrated that treatment with anamorelin HCl provides the following benefits:

- Increase in lean body mass (LBM) demonstrating anabolic effects
- Significant increases in body weight and/or lean body mass are observed in patients with cancer anorexia-cachexia when treated at dose levels of 50 or 100 mg once daily. Increase in total body mass that is driven by LBM and fat mass to a lesser degree, which demonstrates restoration of the metabolic abnormalities of cachexia and provides increased adiposity for energy
- Improvement of anorexia-cachexia symptoms/concerns (via FAACT domain scores), including symptoms related to loss of appetite and early satiety, and concerns related to weight, body image and general health
- Improvement of LBM and body weight correlated to improvement in patient concerns and symptoms related to anorexia-cachexia (FAACT)
- Greater number of LBM responders at Week 12
- Biologic activity is evident as assessed by responses for both IGFBP-3 and IGF-1; the increase in IGFBP-3 is greater than the increase observed in IGF-1.

Clinical data from multiple Phase 1 studies and Phase 2 studies showed that administration of anamorelin HCl at doses of 50-100 mg daily resulted in significant, rapid, and sustained increases in appetite, increases in food intake, GH release, stimulation of IGF-1 and/or IGFBP-3 levels, and significant increases in body weight. A good safety and tolerability profile was seen with multiple doses up to 150 mg and single doses up to 400 mg. A dose of 100 mg anamorelin HCl was selected for the Phase 3 program since this dose level was found to be well-tolerated and was shown to lead to greater weight gain in NSCLC patients than the 50 mg dose after 12 weeks of treatment (mean placebo-adjusted weight gain of 1.47 kg versus 1.02 kg, respectively, corresponding to approximately 45% greater weight gain at 100 mg/day than at 50 mg/day).

At least three other molecules with related mechanisms of action have undergone fairly extensive clinical testing: ibutamoren (MK-677) (Patchett, Nargund et al. 1995), tabimorelin (NN-703) (Zdravkovic, Sogaard et al. 2000), and capromorelin (CP-424,391) (Pan, Carpino et al. 2001). Development of ibutamoren and capromorelin were both suspended, presumably as a result of the inability to demonstrate meaningful benefits in the "frail elderly" setting. There are no reports of either agent being studied in the cancer anorexia, cachexia or unintended weight loss indication proposed for anamorelin HCl although a study with ibutamoren clearly demonstrated the proof-of-concept for reversing catabolism in a starvation model. Anamorelin HCl offers the promise to fulfill this important therapeutic role of treating anorexia, cachexia or unintended weight loss in NSCLC patients.

D. PATIENT RECRIUTMENT

Patients with advanced cancer will be recruited from The University of Texas MD Anderson Cancer Center (UTMDACC; a comprehensive cancer center). At UTMDACC, 38 patients will be recruited from medical oncologists working in the outpatient centers (including Gastrointestinal, Thoracic Oncology, and Melanoma) and the clinics based in our own department (Supportive Care, Integrative Medicine, Cachexia, and Rehabilitation clinics). Patients will be screened for eligibility criteria and the FACIT-F and HADS will be administered after research staff has obtained verbal consent from the patient. Patients who are found eligible after screening will be asked to participate in the study. Written informed consent will be obtained by the research staff and study assessments will be administered.

ELIGIBILITY:

Inclusion Criteria:

a) Patient with a diagnosis of advanced cancer (metastatic or recurrent incurable solid tumors excluding prostate cancer)
b) Presence of fatigue on FACIT-F subscale of ≤ 34 on a 0 to 52 scale [in which 52 = no fatigue and 0 =worst possible fatigue];
c) Patient should describe fatigue as being present for a minimum of 2 weeks prior to screening;
d) CRP must be ≥ 3mg/l* in the absence of any other more likely cause of increased CRP like an infection or an autoimmune disorder.
e) No evidence of moderate to severe depression as determined by a HADS depression score of ≤13
f) Presence of unintentional weight loss ranging from ≥ 2 - ≤15% at any time within the last 12 months
g) Uncontrolled pain; If patient is on opioids for the treatment of cancer pain, he/she must have had no major dose change (>25%) for at least 48 hours prior to study entry. The dose of morphine equivalent daily should not exceed 120mg/day unless approved by the PI. Change in opioid dose after study entry is allowed;
h) Patient must be 18 years of age or older. The questionnaires used in this study have been validated only in the adult population;
i) Patient must be willing to engage in telephone follow up with research staff;
j) Patient must have telephone access to be contacted by the research staff;
k) Hemoglobin level of >/=9 g/dL
l) Estimated life expectancy of > 4 months at the time of screening.

m) Adequate hepatic function, defined as aspartate transaminase (AST) and alanine transaminase (ALT) levels ≤ 5 × upper limit of normal (ULN)

Exclusion Criteria:

a) Major contraindications to anamorelin .e.g. hypersensitivity;
b) Regularly engaged in moderate or vigorous-intensity exercise for at least 5 times a week
c) Inability to complete the baseline assessment forms or to understand the recommendations for participation in the study.
d) Pregnant or lactating women, childbearing age women who are not on birth control. Negative pregnancy test for women of childbearing potential, as defined by intact uterus and ovaries, and a history of menses within the last 12 months. Pregnancy test to be performed no greater than 14 days prior to consent in study. In cases of women with elevated b-HCG, these candidates will be eligible to participate so long as the level of b-HCG is not consistent with pregnancy. Women of childbearing potential need to be on or use contraception, or be abstinent during the study period. Their male partners must also use contraception (condom) or maintain abstinence.

   Birth controls specifications: Women who are able to become pregnant must use birth control during the study and for 30 days after the last Anamorelin dose. Acceptable forms of birth control include barrier methods (such as condom or diaphragm) with spermicide.
e) Uncontrolled diabetes mellitus (Fasting Blood Sugar >200mg/dl) at screening
f) Male patients with a history of untreated hypogonadism
g) Patients on drugs with strong CYP 3A4 inhibitors within the previous two weeks (ketoconazole, clarithromycin, itraconazole, nefazodone, telithromycin)
h) Patients on drugs that may prolong the PR or QRS interval durations, such as any of the Class I/Sodium (Na+) Channel blocking antiarrhythmic medications should be avoided (e.g. Flecanide, Procainamide, Propafenone, Quinidine).
i) Patients with untreated clinically relevant hypothyroidism
j) Patients currently on investigational therapies will be evaluated by the PI on a case by case basis and study participation approval will be obtained from the treating oncologist.
k) Patients with prostate cancer

* CRP is a biomarker for fatigue in palliative care patients hence was used as eligibility criteria. Recent studies suggest 3mg/dl as an ideal cut off for significant inflammation (2017, 2017, Amano, Maeda et al. 2017, Paulsen, Laird et al. 2017).

Birth Control Information

Taking part in this study can result in risks to an unborn or breastfeeding baby. Patients should not become pregnant, breastfeed a baby, or father a child while on this study. Sexually active patients must use birth control during the study.

Birth Control Specifications: Women who are able to become pregnant must use birth control during the study and for 30 days after the last Anamorelin dose.

Acceptable forms of birth control for men and women include barrier methods (such as condom or diaphragm) with spermicide, or abstinence.

Males must tell the doctor right away if their partner becomes pregnant or suspects pregnancy.

Pregnant women will not be enrolled on this study. If the patient becomes pregnant or suspects that she is pregnant, she must inform her doctor right away.
Pregnancy may result in removal from this study.

E. PHARMACEUTICAL INFORMATION

IND Agent: Anamorelin HCl 100mg Tablet (Refer to Investigator Brochure for further information)

Chemical Name: The chemical name for anamorelin hydrochloride is (3*R*)-1-{(2*R*)-[(2-amino-2-methylpropanoyl)amino]-3-(indol-3-yl)propanoyl}-3-benzyl-*N*,*N*',*N*'-trimethylpiperidine-3-carbohydrazide hydrochloride.

Other Names:
RC-1291, RC-1291 HCL, NNC 26-1291, NNC0026-0000-1291, 26-1291

Mode of Action: Anamorelin HCl is an orally active selective ghrelin receptor agonist.

Description: Anamorelin HCl 100mg tablet are immediate release. The anamorelin HCl 100 mg tablets are coated, yellow, and have a caplet shape (0.292" x 0.675") debossed with the characters "HE2". Previous 100 mg tablets were debossed with the characters "HLS". The 100 mg tablets are formulated with microcrystalline cellulose, croscarmellose sodium, colloidal silicon oxide and magnesium stearate, and are coated with Opadry® II yellow color.

How Supplied: Helsinn will supply Anamorelin HCl to the site. The tablets are packaged as 30 tablets per bottle.

Note: Anamorelin HCl may be repackaged from the supplied bottles and dispensed in pharmacy dispensing bottles according to the quantities specified by the investigator.

Storage: The recommended long-term storage condition for anamorelin HCl tablets is USP controlled room temperature. Store at 20-25 °C (68-77 °F). Excursions permitted to 15-30 °C (50-86 °F).

Stability: Anamorelin HCl has a shelf-life of 4 years from date of manufacture.

Route(s) of Administration: Oral

Method of Administration: It is recommended patients should take Anamorelin HCL 100mg (1 tablet) orally while fasting at least 1 hour before the first meal of the day.

Safety Profile/Potential Side effects: Anamorelin 100mg may cause increased blood glucose levels, glucose urine present, glycosuria, increased glycosylated hemoglobin, hyperglycemia, and Diabetes (Diabetes mellitus, diabetes mellitus inadequate control, and type 2 diabetes mellitus). In addition, it may cause hypertriglyceridemia and increased transient ALT/AST.

Potential Drug Interactions: **CYP3A4 Interactions:**
Anamorelin HCl is mainly metabolized by CYP3A4 (99.67%), and the CYP2C8 (0.27%) and CYP2D6 (0.05%) metabolic pathways are minor. Plasma concentrations of anamorelin have been shown to be increased by ~3-fold in the presence of ketoconazole (a CYP3A4 inhibitor) and to be decreased by ~3-fold in the presence of rifampin (a CYP3A4 inducer). Anamorelin HCl should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. Strong CYP3A4 inhibitors should be avoided, such as ketoconazole, clarithromycin, itraconazole, nefazodone, and telithromycin. Furthermore, the concomitant administration of anamorelin with strong CYP3A4 inducers such as rifampicin should also be discouraged, as it may result in a reduction of the clinical effect. Refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ or Appendix Y for a reference list for interaction table.

Co-administration with Other Drugs
The administration of anamorelin HCl with agents that may prolong the PR or QRS interval durations, such as any of the Class I/Sodium (Na+) Channel blocking antiarrhythmic medications should be avoided (e.g. Flecanide, Procainamide, Propafenone, Quinidine).

Concomitant and Prohibited Medication

- Concomitant medications must be recorded from 28 days prior to the first dose of study drug through the last dose of study drug.
- There is no rescue therapy for fatigue.
- As specified within the Inclusion criteria, if a patient is on opioids for the treatment of cancer pain, he/she must have had no major dose change (>25%) for at least 48 hours prior to study entry. The dose of morphine equivalent daily should not exceed 120mg/day. Change in opioid dose after study entry is allowed
- As specified within the Exclusion Criteria, strong CYP 3A4 inhibitors are prohibited within the two weeks prior to first dose. If a patient is required to take a strong CYP3A4 inhibitor while enrolled in this trial, they must be discontinued.
- As specified in the Exclusion Criteria, the administration of any drugs that may prolong the PR or QRS interval durations, such as any of the Class I/Sodium (Na+) Channel blocking antiarrhythmic medications (e.g. Flecanide, Procainamide, Propafenone, Quinidine) are prohibited. If a patient is required to take any of these drugs while enrolled in this trial, they must first be discontinued.

Drug Accountability:

Agent Ordering:
Helsinn will ship the medication to the Investigational Pharmacy Services. Drug re-ordering will be via a drug order form or electronic/fax communication with the sponsor representatives.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a record of the inventory and disposition of all agents received from Helsinn. Sites may use their own drug accountability logs per their standard procedures. Drug Accountability records will capture Lot numbers dispensed to the patient. Unused drug at the remainder of the trial and expired drug may be destroyed on site per the site's drug expiration policy or the sponsor will make arrangements for destruction.

Patient Pill Diary Assessment: Patient will be provided with a pill diary to track compliance. The diary will be reviewed by the study team at designated visit for compliance review. If > 5 consecutive doses over a 6 week period are missed a deviation will be filed for the patient. Medication will be reconciled and disposed of according to the Site's standard procedure for Patient Medication Reconciliation.

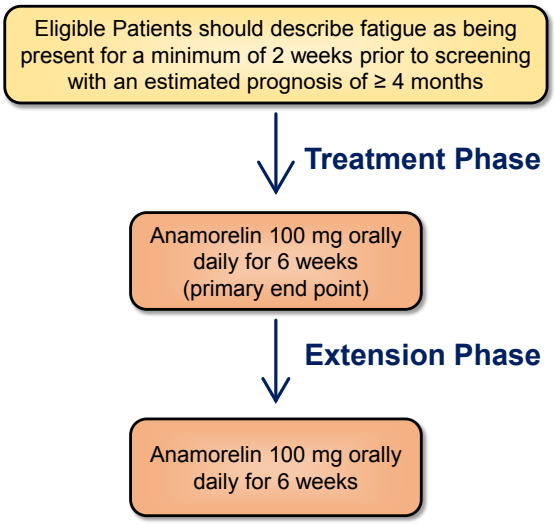
Dose: Dose will be 100mg PO Daily. 100 mg tablets will be used in this study. No other tablet strengths are available and there are no permitted dose reduction schemes. Dosing may be delayed/interrupted at the discretion of the Investigator if needed due to an adverse event, and discussed with the patient. Study drug may be re-started at the original dose level when the adverse event returns to grade 1 or less in severity. If the study drug is interrupted for more than 7 consecutive days, the patient should be discontinued. Study drug should not be interrupted or discontinued for disease progression unless an adverse event occurs which necessitates discontinuation.

F. RESEARCH DESIGN AND METHODS

In this single arm study, 38 patients will be treated with anamorelin for 6 weeks with an optional extension phase of 6 more weeks based on PI judgment of tolerability and safety and patient willingness. Patients will receive anamorelin and physical activity for 6 weeks for the intervention phase. The patient may choose to receive anamorelin and physical activity for an additional 6 weeks in the optional extension phase. Patients will be followed for toxicity evaluation for 4 weeks after the 6-week treatment phase.

Treatment plan (see treatment schema below)
In the proposed study we plan to use **anamorelin 100mg tablets** [Helsinn Therapeutics, Iselin, NJ]. Patients should take 1 tablet orally while fasting (at least 1 hour before a meal), and preferably in the evening.

See Table 2 for the study assessments. All patients receiving the study drug anamorelin will receive a standardized exercise prescription and nutritional support (high calorie and amino acid diet) at the MDACC Supportive Care Center [See appendix Q, R]. The rationale for standardized physical activity and nutritional support is that these two interventions are important covariates for the management of fatigue (Saligan, Olson et al. 2015) in addition to pain and psychological symptoms such as pain, anxiety, and depression (which are controlled for in the eligibility criteria).



Treatment Schema

Exercise Prescription: This exercise prescription is based on the American College of Sports Medicine (ACSM) exercise recommendations for cancer survivors to ensure safety and maximal benefit. (Schmitz, Courneya et al. 2010).

The exercise intervention will include (a) resistance training 3 days/week and (b) moderate intensity walking for up to 150 minutes per week. At the first supervised session the patient will perform the resistance exercises and moderate intensity walking up to 30 minutes, depending on the patient's tolerance. Participants will have consultation sessions by telephone on Days 8, 15, 29, and 36 with an ACSM-certified cancer exercise specialist to clarify any questions participants may have and to check compliance with the exercise regimen.

The resistance exercise program has been designed to strengthen the major muscles of the lower body, including the quadriceps, hamstrings, gluteus maximus, and hip flexor group. These exercises will include (but will not be limited to) squats, lunges, leg extensions, leg curls, and hip extensions. We will use resistance tubes as our mode of resistance. These tubes are color-coded to indicate their specific resistance level: light, moderate, or hard. The resistance exercise sessions are to be completed 3 days a week, allowing at least 48 hours between each session. The participant will begin with 1 set of 10 to 12 repetitions at the lightest resistance progressing to 2 sets of 12 repetitions as exercise tolerance increases. Resistance will then be increased as the participant's endurance and strength progresses. For the graded resistance program the individual begins with a lighter resistance and progresses to heavier resistance once a level has been mastered. The participant will begin with 2 sets of 12 repetitions at the next established intensity level.

Since the level of aerobic fitness will vary among participants, the frequency and duration of the walking program will be established based on the exercise physiologist's assessment of the participant's baseline aerobic fitness level (six-minute walk test). For example, the recommendation may be to walk 10 minutes 1-3 times a day or up to a 30-minute walk once a day at a moderate intensity level. Participants will work toward the goal of 150 minutes of moderate intensity walking per week.

To encourage and monitor adherence to the walking program, we will provide participants with a pedometer and an exercise log to record their resistance exercise sessions, time spent in moderate intensity walking, and the number of steps they take each day. Participants will be asked to walk a minimum of 5 days a week at the duration established by the exercise physiologist. In the first week of the intervention, the exercise physiologist will meet with each participant to evaluate his or her current strength and aerobic fitness level and to teach the assigned exercises. Each week the exercise physiologist will assess their progress and help them identify and overcome any barriers to completing the exercise program, and to evaluate for adverse events or health problems. The frequency, intensity, and duration of the assigned exercises will also be evaluated and adjusted as necessary.

Nutrition counseling

All patients enrolled in this study will receive at baseline and day 21(± 3) nutritional support by a dietitian. The plan would be to achieve a goal of 1.5x Resting Energy Expenditure (REE) estimated by the Mifflin St. Jeor method (Mifflin, St Jeor et al. 1990). Frequent small meals that are calorie dense will be recommended. Patients with taste disturbance will be given a trial of Zinc 220mg orally daily for 4 weeks.

Commercially available specific amino acids preparations rich in arginine, glutamine, and leucine-related products such as Beta hydroxyl Beta methylbutyrate, may be prescribed as advised by a dietitian to assist patients achieve calorie goals and maintain lean body mass(Molfino, Gioia et al. 2013) (Molfino, Gioia et al. 2013).

A subsample of 15 patients will be asked to complete online dietary logs. Participants will be asked to keep diet records for up to 5 days prior to starting treatment and up to 5 days during the last week of treatment. Diet records will be kept by paper/pen or electronically using a mobile application (MyFitnessPal) designed for food tracking (participant preference). Participants and/or their caregivers will be instructed on how to keep food records by trained Bionutrition Research Core staff. Participants will be asked to record their food and calorie-containing beverage intake at the time of consumption with a notation of the time when the foods/beverages were consumed. Records will be entered and analyzed with Nutrition Database System for Research software by trained Bionutrition Research Core staff. Photographs of foods/beverages consumed will be optional but, when available, will assist with nutrition analysis.

G. OUTCOME MEASURES/PLANNED ASSESSMENTS

- **PRIMARY: To evaluate changes in the Functional Assessment of Cancer Illness Therapy-Fatigue (FACIT-F) subscale score at Day 43± 3 days compared to baseline in patients with advanced cancer receiving oral anamorelin 100mg daily and standardized physical activity and nutritional counseling.**

FACIT-F is a well-validated QOL instrument in cancer patients (Cella, Tulsky et al. 1993). This FACIT-F fatigue subscale was chosen as the primary outcome measure since it has been widely used in CRF treatment trials by our team and by others (Bruera, Driver et al. 2003, Bruera, Valero et al. 2006, Bruera, El Osta et al. 2007, Minton, Richardson et al. 2008, Yennurajalingam, Frisbee-Hume et al. 2012). The 13-item fatigue subscale is a patient-rated assessment of intensity of fatigue and its related symptoms on a scale of 0 to 4. This scale has been shown to have strong internal consistency (α = 0.93–0.95), sensitivity of 0.92, and specificity of 0.6923 (Cella, Tulsky et al. 1993).

- **SECONDARY: To examine the effects of anamorelin and standardized physical activity and nutritional counseling on Health-related quality of life and patient reported outcomes as measured by**

The Multidimensional Fatigue Symptom Inventory-Short Form[MFSI-SF], PROMIS –Fatigue, Hospital Anxiety Depression Scale (HADS), Edmonton Symptom Assessment Scale (ESAS), Functional Assessment of Cancer Therapy (FACT-G), and its Functional Assessment of Anorexia/Cachexia Treatment (FAACT) subscale in these patients.

To examine the side effects and tolerability of anamorelin in these patients

MFSI-SF consists of 30 items designed to assess the multidimensional nature of fatigue(Stein, Jacobsen et al. 2004). Ratings are summed to obtain scores for 5 subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor).

PROMIS measures key symptoms and health concepts applicable to advanced cancer, enabling efficient and interpretable clinical trial research and clinical practice application of patient-reported outcomes (PROs) (Rothrock, Hays et al. 2010, Yost, Eton et al. 2011). The PROMIS fatigue measure used in the study was found to be highly correlated with the legacy measures (Barsevick, Irwin et al. 2013).

HADS: Depression symptoms will be assessed at the time of screening for the patient to be enrolled in the protocol using the 14-item HADS questionnaire. This questionnaire asks patients to underline the statement that most closely matches how they have been feeling in the previous week. This questionnaire has been found to be valid and reliable in a number of clinical situations and has been widely used in medically ill patients (Johnston, Pollard et al. 2000).

The **FACT-G** is a 27-item compilation of general questions divided into four primary domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. It is appropriate for use in patients with any form of cancer, and extensions of it have been used and validated in other chronic illness conditions as well (Cella, Tulsky et al. 1993, Webster, Cella et al. 2003). The FACT-G is the first 2 pages of FACIT-F.

The **FAACT-Anorexia/Cachexia** subscale is a 12-item symptom-specific subscale designed to measure patients' additional concerns about their anorexia /cachexia during the previous 7 days. The FAACT has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.88 for the 12 components (Ribaudo, Cella et al. 2000). Patients rate the intensity of anorexia/cachexia and its related symptoms on a 0-4 scale like that used in the FACIT-F.

The **ESAS** measures 10 common symptoms in the past 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being); This questionnaire has been found valid and reliable in cancer populations (Bruera, Kuehn et al. 1991).

○ **EXPLORATORY: To explore the effects of anamorelin and standardized physical activity and nutritional counseling on muscle function (as measured by the 30 second chair stand test, 6 minute walk test, day time activity (accelerometer), body composition (as measured by INBODY), and Resting Energy Expenditure (measured by indirect calorimetry)**

Measures: We will use the **30 second chair stand test**, six-minute walk test, and an accelerometer. A self-report exercise questionnaire, the Godin leisure-time physical activity questionnaire, will be used to complement the objective measures. IM Systems-three dimensional accelerometers ("Biotrainer-Pro") will be used to objectively measure physical activity. These accelerometers complement the self-report for estimating physical activity and can record physical activity in 15-second increments for 5 days. Patients will wear the accelerometer for 5 days during the week before each assessment. When participants return the accelerometers the data will be uploaded into the project database, and the amount of time spent in moderate to vigorous activity will be calculated.

Physical Performance Tests: The 30 second chair stand test, 6-minute walk test, and Godin leisure-time physical activity questionnaire will be administered at baseline and on Day 43. The 30 second sit-to-stand task assesses lower body strength (Rikli and Jones 1999). A standard chair without arms with an approximate height of 17 inches will be used. After a demonstration, a practice trial of one repetition will be done to check for proper form. On the start signal, the participant rises to a full stand and then returns to a fully seated position. The patient completes as many full stands as possible within a 30 second period.

In the six-minute walk test, participants are asked to walk as fast and as far as they can for six minutes, and the distance walked is measured. The test will be conducted in an area with a 250-foot hallway and minimal traffic. The six-minute walk test has high test-retest and inter-tester reliability, and its validity is supported by correlations with self-report measures of fatigue and functional status (Simmonds 2002). The patient will be strongly encouraged to give a maximum effort. The six minute walk test will be performed as per the ATS guidelines (https://www.thoracic.org/statements/resources/pfet/sixminute.pdf.)

The Godin leisure-time physical activity questionnaire asks participants how many times per week on average do they participate in strenuous, moderate and mild exercises for more than 15 minutes during their free time. It also asks how often the participant engages in regular activity long enough to work up a sweat during their leisure time in a typical week (often, sometimes, never/rarely).

Body Composition: All patients will be assessed for lean body mass, skeletal muscle mass, extracellular water/ total body water body, fat mass, body fat mass, and whole body phase angle evaluation (using the InBody body composition scale) (Dalal, Hui et al. 2012, Del Fabbro, Parsons et al. 2012, Yennurajalingam, Willey et al. 2012, Hui, Bansal et al. 2014). Resting energy expenditure will be assessed at baseline and Day 43±3 days, and at the end of 6 weeks of the extension phase.

- **EXPLORATORY: Potential inflammatory biomarkers of cancer-related fatigue (CRF) [C-Reactive Protein (CRP), intracellular cytokines monocyte IL-6 and IL-6 Receptor, TNF-α & TNF-α Receptor, IL-10, IL-8, IL-1b&RA, and IGF-1]**

Cytokine assessments: Peripheral blood will be collected at baseline, Day 21(± 3) and Day 43(± 3) (Table 2). On completion of the study, the change in levels of synthesis of cytokines in LPS-induced monocytes will be correlated with the proportion of patients with decreased fatigue and with those who have no decrease in fatigue. Methods: Briefly, 1 mL of peripheral blood will be incubated with 10 µg/mL LPS for 5 h and with brefeldin A for the last 3 h of incubation to block the intracellular transport of the de novo cytokine synthesis from the Golgi. Thereafter, LPS-activated monocytes will be stained for surface expression of CD14 and CD33 and for the presence of cytoplasmic cytokines, as previously described (Reuben, Lee et al. 2000), by using a panel of cytokine-specific monoclonal antibodies conjugated with phycoerythrin to detect one of the cytokines. C-reactive protein a surrogate marker for inflammation will be assessed at baseline, Day 21 and Day 43 similar to cytokines. Correlative blood samples will be destroyed after completion of analysis.

Global Symptom Evaluation: On Day 43(±3), patients will be asked about their fatigue (worse, about the same, or better) after starting the intervention. If patient answers “better”, we will ask the patient to select how much better: “almost the same, hardly better at all, a little better, somewhat better, moderately better, a good deal better, a great deal better, or a very great deal better”. If the patient answered “worse”, we will ask them to select how much worse: “almost the same, hardly any worse at all, a little worse, somewhat worse, moderately worse, a good deal worse, a great deal worse, or a very great deal worse”.

- **EXPLORATORY: to explore effects of anamorelin on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI)**

The **PSQI** is a 19-item questionnaire that is an effective instrument in measuring the quality and patterns of sleep(Buysse DJ 2006).It differentiates "poor" from "good" sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. Each area is rated from 0-3 with the higher score reflecting more severe sleep complaints. The addition of all scores permits the analysis of the participant's overall sleep experience. The PSQI can be used for both an initial assessment and ongoing comparative measurements across all healthcare settings. The PSQI has internal consistency and a reliability coefficient (Cronbach's alpha) of 0.83 for its seven components. Numerous studies using the PSQI have supported high validity and reliability. The PSQI global score ranges from 0 to 21, with a score of 5 or greater indicating significant sleep disturbance.

A total of 10 subjective questionnaires will be administered to patients. All questionnaires are mandatory because we will use the data obtained for effect size calculations to achieve the objectives of this study.

	Table 2. Study assessments									
ASSESSMENTS	Screening (within 28 days of enrollment)	Baseline (within 28 days of enrollment)	Day 8* (± 3)	Day 15* (± 3)	Day 21* (± 3)	Day 29 (± 3)	Day 36* (±3)	Day 43* (± 3)	Phone F/U after Day 71(± 5)	6 Week extension phase‡ (± 5)
Pregnancy Test*	X									
History/ Physical exam	Documentation of Advanced cancer	X						x		
Zubrod score		X						x		X
Medication review		X	X	X	X	X	X	X		X
HADS, FACIT-F subscale, FACT-G,FAACT subscale, MFSI-SF, PROMIS-Fatigue	HADS & FACIT-F subscale only	X	x	X	x	X	x	X		X
PSQI		X				X		X		X
ESAS	X	X		X		X		X		X
Physical Performance Tests (30-second chair stand test, six-minute walk test, accelerometer, Godin leisure-time physical activity questionnaire)		X						X		X
Body composition Body Mass Index (InBody), Resting energy expenditure using indirect calorimetry§	X^	X						x		X
Cytokines (Serum IL-1b, TNF-α, IL-6; Intracellular cytokines IL-6 R; TNF R, IL-1R, IL-10);		X			X			x		x
Electrolytes, IGF-1		X			X			X		X
Hemoglobin, liver function tests, PT/INR, C-Reactive Protein (CRP)	X				X			X		X
Pre-albumin/Albumin		X			X			X		
Fasting Blood Sugar	X				X			X		
Toxicity evaluation#			X	X	X	X	X	X	X	X
Global Symptom Evaluation								X		
Physical Activity		X@	x	x	x@	x	x	x		x
Nutrition Counseling/Diet record collection+		x@+			x@			x+		

‡ Optional extension phase
***** Pregnancy test to be performed no greater than 14 days prior to consent in study.
@ Supervised sessions with an ACSM-certified cancer exercise specialist and meetings with dieticians will occur at the same time as these scheduled visits;
^ documentation of weight loss ranging from ≥ 2 - ≤15%
#Toxicity Evaluation: Toxicity evaluation as per NCI CTC AE v.04 criteria will be determined by the PI, physical exam and laboratory testing including electrolytes, hemoglobin, liver function tests and PT/INR will be performed as per study assessment in Table 2.
+ Diet Record Collection up to 5 days prior to baseline and up to 5 days during the last week of treatment.

Patients who are unable to return to UTMDACC will have their blood collected by their local physician and the results sent to the UTMDACC study team. The PI/treating physician will review the outside labs, determine clinical significance, and sign/date the results.

Patients will receive a $15 parking voucher for each visit at Baseline, Day 21 when they meet with the exercise specialist and nutrition counselor, Day 43 when they return to perform the physical performance tests, and at the end of the extension phase when the patient returns to perform the physical performance tests (if in the best interest of the patient). Patients will receive up to 4 parking vouchers, for a total of up to $60. They will be asked to present their parking ticket to the study coordinator at the clinic visit and will be provided a parking voucher.

Fasting Blood Sugar (FBS) – If FBS is greater than CTCAEv4 Grade 3, Anamorelin will be held and restarted in 3 days once blood sugar returns to normal. We will re-check blood sugar in 1 week. If FBS is still elevated (>250mg/dl), we will hold Anamorelin for 1 week. If FBS remains elevated (>250mg/dl), the patient will be withdrawn from the study.

Source Documentation: All patient data will be recorded directly on the case report forms and will be considered source data.

The Investigator or physician designee is responsible for providing source documentation and assigning attribution for all AEs.

H. SUBJECT COMPLIANCE

Site personnel will assess treatment compliance at each visit during the treatment period using the patient's pill diary and by the patient returning the unused study medication and/or empty study medication bottle.

I. PATIENT WITHDRAWAL CRITERIA

Patients may withdraw their consent at any time and discontinue the study. Patients may also be discontinued from the study at any time for the following reasons:

- Adverse event requiring cessation of study drug (adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug)
- Major protocol violation (patient lost to follow-up, if the study drug is interrupted for more than 7 consecutive days, hospitalization resulting from major side effects, lack of consent, lack of safety laboratory tests)
- Lost to follow-up (Note: site must make every effort to follow all randomized patients including contact of family members and/or other medical facilities to avoid losing patients to study follow-up)
- Death
- Patients should be encouraged to complete the Day 43 visit procedures if they withdraw prematurely in order to collect final study assessments.

- For patients who experience an adverse event requiring cessation of study drug, they will be followed until the event resolves, until they begin another clinical trial, or until the end of the study. However, certain adverse events (e.g., a cerebrovascular accident, worsening hypertension) will not be expected to resolve completely; in these cases, the date and time should be recorded when the event reaches its new, stable equilibrium and any remaining residual of the event should be documented.
- We will add replacement patients to account for withdrawals until we reach 38 total patients.

Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

- Seriousness
  For each AE, the seriousness must be determined according to the criteria given in Section J below

- Intensity
  The intensity of the AE is classified according to the CTCAEv4.0. Grade refers to the severity (intensity) of the AE:

  CTCAEv4 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

  CTCAEv4 Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

  CTCAEv4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

  CTCAEv4 Grade 4: life-threatening consequences; urgent intervention is indicated.

  CTCAEv4 Grade 5: death due to an AE.

Expected adverse events such as vomiting, nausea, diarrhea, constipation, asthenia, hyperglycemia, blood sugar <200 mg/dl and AEs assessed as Grades 1 and 2 will not require reporting to Helsinn. Expected adverse events will be tracked and submitted during annual review. Adverse events (including event name, grade, start/stop date and attribution) will be entered into OneConnect, which will serve as the source documentation for adverse events. The Principal Investigator or physician designee will verify the attribution assigned in OneConnect by signing the OneConnect adverse events printout at the end of protocol treatment. Prometheus will be used as the electronic case report form for this protocol.

AEs Grade 3 or higher that are at least possibly treatment-related will trigger the toxicity monitoring rule. Based on the phase 3 trial published in Lancet Oncology (Temel, Abernethy et al. 2016) we will closely monitor hyperglycemia, diabetes, and nausea.

Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information.

The causality assessment should be done separately for each study treatment.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no". An assessment of "no" would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):
- Subject's response after de-challenge or subject's response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

J. SERIOUS ADVERSE EVENTS (SAE) REPORTING LANGUAGE FOR MD ANDERSON-SPONSORED IND PROTOCOLS

As stipulated in 2.6 of the Strategic Collaboration Agreement, MD Anderson is the sponsor and assumes all obligations regarding the preparation and submission of individual and aggregate safety reports to FDA, Ethic Committee, and other relevant persons to the extent required by and as per the applicable US laws, regulations, and guidelines. The PI will forward to Helsinn any serious adverse reaction (i.e. for which it is judged there is a reasonable causal relationship between the study drug and the adverse event), regardless of its expectedness, within 24 hours from first awareness, including follow-ups.

The PI shall provide Helsinn with relevant safety data including study and IND safety reports (prior to their finalization) and any safety signal or risk (with the rationale) originating from the study. The e-mail address for exchanging all the above-mentioned safety information is: drug-safety@helsinn.com.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Adverse events will be captured according to the recommended AE recording guidelines for a Phase II protocol.

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30-day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

K. OUTSIDE PHYSICIAN PARTICIPATION DURING TREATMENT

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix Z).
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
6. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
7. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
8. Patients will return to MDACC every month for evaluation.

L. STATISTICAL CONSIDERATIONS

In this single arm study, the primary end point is the difference between the FACIT-F subscale score at baseline and Day 43 ± 3 days in the study patients.

Sample size calculation: The most evidence-based treatment for cancer-related fatigue is the use of physical activity. A previous study (Segal, Reid et al. 2009) found a standard deviation of baseline to 12-week differences in FACIT-F subscale scores = 7.5. A study by Cella and colleagues (Cella, Eton et al. 2002) states that differences of 3-5 points or more on the FACIT-F subscale are clinically important differences. This difference ≥ 3.5 points as a responder threshold is well above the placebo response seen in fatigue trial using dexamethasone conducted by our team [the mean (SD) of placebo response was 3.1 (9.59)]. With 30 evaluable patients, we can detect a mean change = 4.0 (assuming Normal data, 80% power and a two-sided 5% alpha,

and a 7.5 standard deviation of differences) using a paired t-test. If we assume that our dropout rate will be no higher than 20% based on our prior fatigue trials, we will recruit 38 patients.

No formal interim analysis is planned for this study. Descriptive statistics of data elements from exploratory assessments (primarily muscle function and body composition) may be summarized at intervals to-be-determined based on study enrollment.

The method of Thall, Simon, and Estey (Thall, Simon et al. 1995) will be employed to perform interim safety monitoring. We will assume a Beta (.3, .7) prior distribution for the DLT rate, which in particular has mean DLT rate of 30%. We will target a 30% DLT rate and we will terminate enrollment into the trial if

Pr{DLT rate > 30%| data} > 0.9

That is, if at any time during the study we determine that there is more than a 90% chance that the DLT rate is more than 30% we will stop enrollment into the study. We will monitor in cohorts of 5. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

[# of patients with DLT/ # of patients evaluated] >= 4/5, 6/10, 8/15, 9/20, 11/25

The operating characteristics of this rule in the trial are shown in the following table:

Operating Characteristics for Safety Monitoring Rule

True DLT Rate	PET	Mean # Pts
10%	0%	30.0
20%	2%	29.6
30%	16%	27.6
40%	51%	22.5
50%	84%	16.2

PET = Probability of Early Termination;
Calculations performed using MultcLean Desktop Version 2.1.0.

We will summarize the demographic and clinical characteristics of all patients enrolled in the pilot study. Mean, standard deviation, median, and range for continuous variables, frequency and proportion for categorical variables will be calculated. We will determine mean change in FACIT-F subscale (primary outcome measure) from baseline to day 43. Similar analyses will be conducted for the secondary outcomes subjective: MFSI-SF, PROMIS-fatigue, FACT-G, FAACT, ESAS symptoms, HADS, Godin Leisure time physical activity questionnaire, PSQI, and Global Symptom Evaluation (GSE); objective: 30 second chair stand test, the six-minute walk test, body composition(lean body mass, skeletal muscle mass, extracellular water/ total body water body, fat mass, body fat mass, whole body phase angle); mean day time activity (accelerometer) and REE; Correlatives cytokines, c-reactive protein and IGF-1. Based on whether the data will be normally distributed (Shapiro-Wilk test) we will use paired t-test or non-parametric equivalents. We will also summarize fatigue scores, other secondary outcomes including ESAS items, and FACT-G at each point in time, and the frequency and type of side effects will be assessed by National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Linear mixed effects models will be used to evaluate fatigue and symptom end points to analyze longitudinal effects. Data will be graphed for analysis and presentation and that additional analyses may be conducted as warranted. Finally, we will also examine the association between change in FACIT-F scores and changes in muscle function, day time activity, and body composition using

correlation coefficients. Given the large number of statistical comparisons proposed, the results of secondary and exploratory analyses will be considered hypothesis generating.

The investigator is responsible for completing an efficacy/safety summary report and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This will be submitted after every five enrolled subjects have completed six weeks of study therapy. A copy of the summary will be placed in the investigator's regulatory binder, under "sponsor correspondence".

M. DATA CONFIDENTIALITY PLAN

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

During the study, trained research staff will be performing study assessments and monitoring the patient carefully throughout the study period. Regulatory monitoring will be provided by the principal investigator, the Institutional Review Board, and the Data Safety and Monitoring Board. Patient confidentiality will be maintained by use of unique study numbers, secure storage of clinical data, and anonymous reporting.

Health information will be protected, and we will maintain the confidentiality of the data obtained from the patient's chart to the best of our ability.

Collection of identifiers: We will collect and securely store patients' identifiers (including name and medical record number). Each patient will be assigned a unique study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Confidentiality will be protected to the best of our ability. All electronic records will be stored on password-protected institution computers behind the institutional firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principal investigator, co-investigators, and research staff will have access to study records.

Data sharing: Study data will only be shared with members of the research team and supporter (Helsinn Healthcare). The data will be kept by the principal investigator and data manager in a locked file cabinet and password-protected computers.

Final disposition of study records: These data will be used only for this research study. Once the research has been completed, PHI will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

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