A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ANAMORELIN HCL FOR THE TREATMENT OF MALIGNANCY ASSOCIATED WEIGHT LOSS AND ANOREXIA IN ADULT PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

Study Number	ANAM-17-20
Protocol Version	Final (v5.0)
Protocol Date	13 Jul 2022
EudraCT No.	2018-002926-22
Sponsor	Helsinn Healthcare SA Via Pian Scairolo 9 6912 Lugano, Switzerland Phone: +41 91 985 21 21 Fax: +41 91 985 21 22
Clinical CRO	PSI CRO AG Baarerstrasse 113a 6300 Zug, Switzerland
CRO for Statistics and Data Management	Business & Decision Life Sciences 141 rue Saint Lambert 1200 Brussels, Belgium

The clinical trial will be conducted, and essential study documentation archived, in compliance with this protocol, applicable SOP's and standards, which incorporate the requirements of the EU Clinical Trials Directive 2001/20/EC or European Regulation 536/2014, whichever applies, FDA Guidance on Conduct of Clinical Trials of Medical products and ICH Guideline for Good Clinical Practice.

Signature Page, Helsinn Healthcare SA

Medical & Scientific Expert, Clinical Research & Development:

_____ _____
(Signature) (Date)

[redacted]

Clinical Operations Lead, Clinical Research & Development:

_____ _____
(Signature) (Date)

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Lead Statistician, Clinical Research and Development:

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Drug Safety Manager, Regulatory Affairs & Drug Safety:

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Medical Writer, Clinical Research & Development:

_____ _____
(Signature) (D

[redacted]

Signature Page, CROs

Signature Page, Study Site Investigator

Study Title

A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of anamorelin HCl for the treatment of malignancy associated weight loss and anorexia in adult patients with advanced non-small cell lung cancer (NSCLC)

Study Number ANAM-17-20

I have read and understood all pages of this clinical trial protocol and appendices and I agree that they contain all information required to conduct this trial. I agree to conduct the trial as outlined in the protocol and to comply with all terms and conditions set out therein. I confirm that I will conduct the trial in accordance with local regulations, ICH GCP guidelines and the provisions of the Declaration of Helsinki. I will direct, assist and oversee sub-investigator(s) and other relevant staff members under my control and will ensure that all trial staff members have access to copies of this protocol and to all information relating to preclinical and prior clinical experience (e.g., Investigator's Brochure), ICH GCP guidelines, local regulations and the Declaration of Helsinki to enable them to work in accordance with the provisions of these documents.

I will use only the informed consent form approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and will fulfil all responsibilities for submitting pertinent information to the IRB/IEC responsible for this trial.

I agree that Helsinn or its representatives or Health Authorities shall have access to any source documents from which (e)CRF information may have been generated.

I agree that all documentation supplied to me by Helsinn and the CRO(s) concerning this trial will be kept in the strictest confidence.

_____ _____

(Signature) (Date)

Printed Name:

Institution:

TABLE OF CONTENTS

GENERAL INFORMATION

Sponsor	Helsinn Healthcare SA Via Pian Scairolo 9 6912 Lugano, Switzerland Phone: +41 91 985 21 21 Fax: +41 91 985 21 22
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Sponsor Medical Expert	**Helsinn Healthcare SA:** [redacted]

Study Project Manager	**Helsinn Healthcare SA:** [redacted] **CRO:** [redacted]
Statistics	**Helsinn Healthcare SA:** [redacted] **CRO:** [redacted]
Data Management	**Helsinn Healthcare SA:** [redacted] **CRO:** [redacted]
Quality Assurance	**Helsinn Healthcare SA:** [redacted]

	[redacted] **CRO**: [redacted]
Clinical Drug Supplies Packaging and Labeling	Catalent Germany Schorndorf GmbH Steinbeisstr. 1-2 D-73614 Schorndorf, Germany
Central laboratory	**Corporate HQ:** Eurofins Central Laboratory Bergschot 71 4817 PA Breda, The Netherlands **US HQ:** Eurofins Central Laboratory 2430 New Holland Pike, D100 Lancaster, PA 17601, USA
Central ECG Reader	eResearch Technology, Inc. 1818 Market Street, Suite 1000 Philadephia PA 19103, USA
Central eCOA Solution	eResearch Technology, Inc. 1818 Market Street, Suite 1000 Philadephia PA 19103, USA

STUDY SYNOPSIS

Study Title	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Anamorelin HCl for the Treatment of Malignancy Associated Weight Loss and Anorexia in adult patients with Advanced Non-Small Cell Lung Cancer (NSCLC)
Study Number	ANAM-17-20
Sponsor	Helsinn Healthcare SA, Via Pian Scairolo 9, 6912 Lugano, Switzerland
Countries and Sites	Multi-center international study, with sites including, but not limited to, North America and Europe
Clinical Phase	Phase 3
Indication	Treatment of malignancy associated weight loss or anorexia in patients with NSCLC
Study Design	Multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of anamorelin HCl. Approximately 316 patients with advanced NSCLC with cachexia will be randomized 1:1 to anamorelin HCl 100 mg or placebo, taken orally once daily (QD) for a total of 24 weeks. Patients 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 and improvement in anorexia symptoms. Secondary: To evaluate the safety and tolerability of anamorelin HCl, and to further evaluate anamorelin efficacy profile.
Treatment Groups	Group 1 / Test group – 100 mg anamorelin HCl (administered as 100 mg tablets in the fasted condition) Group 2 / Control group – Placebo (administered as matching placebo tablets in the fasted condition)
Drug Administration	Patients will take 1 tablet on Day 1 (if a fasting state is not possible on Day 1, the patient will start study drug on Day 2) and daily thereafter until Visit 10 (Week 24). Patients will be supplied with study drug and re-supplied at Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), Visit 7 (Week 15), Visit 8 (Week 18), and Visit 9 (Week 21). 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	Total of 24 weeks double-blind treatment with anamorelin or placebo. A follow-up telephone visit is scheduled at Week 26.
Number of Patients	A total of 316 patients with advanced NSCLC with cachexia will be randomized 1:1 to anamorelin HCl 100 mg or placebo (158 patients per treatment arm).
Target Study Population	Advanced NSCLC adult patients with body mass index < 20 kg/m^2 with involuntary weight loss of >2% within 6 months prior to screening and anorexia
Inclusion Criteria	1. Signed written informed consent. 2. Female or male ≥18 years of age. 3. Documented histologic or cytologic diagnosis of American Joint Committee on Cancer (AJCC) Stage III or IV NSCLC. Stage III patient must have unresectable disease. 4. Body mass index < 20 kg/m^2 with involuntary weight loss of >2% within 6 months prior to screening. 5. Ongoing problems with appetite/eating associated with the underlying cancer, as determined by having score of ≤ 17 points on the 5-item Anorexia Symptom Scale and ≤ 37 points on the 12-item FAACT A/CS. 6. Patient receiving or not receiving systemic anti-cancer treatment at the time of screening are eligible to participate. Systemic anti-cancer treatment includes first, second, third treatment line with chemotherapy/radiation therapy, immunotherapy or targeted therapy. Patient not receiving systemic anti-cancer treatment is eligible if: a. Not planning to receive anti-cancer treatment and/or at least 14 days must be elapsed from the completion of prior treatment at the day of screening, in case underwent previous cycle, OR b. Planning to receive anti-cancer treatment within 14 days from randomization and/or at least 14 days must be elapsed from the completion of prior treatment at the day of screening, in case underwent previous cycle, OR

	c. Patient on palliative care treatment. 7. ECOG performance status 0, 1 or 2 at screening (see APPENDIX 1). 8. AST (SGOT) and ALT (SGPT) ≤ 3 x ULN or if hepatic metastases are present ≤ 5 x ULN. 9. Adequate renal function, defined as creatinine ≤ 2 × ULN, or calculated creatinine clearance >30 ml/minute. 10. Female patient shall be: a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having a negative urine pregnancy test within 24 hours prior to first dose of investigational product*. Notes: a) Female patient of non-childbearing potential is defined as being in post-menopausal state since at least 1 year; or having documented surgical sterilization or hysterectomy at least 3 months before study participation. b) Reliable contraceptive measures include implants, injectables, combined oral contraceptives, intrauterine devices, vasectomized partner or complete (long term) sexual abstinence. 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 1). *Inclusion criterion #10 will be re-checked and verified at Day 1 (Visit 2).
Exclusion Criteria	1. Patient with other forms of lung cancer (e.g., small cell, neuroendocrine tumors). 2. Woman who is pregnant or breast-feeding. 3. Reversible causes of reduced food intake, as determined by the Investigator*. These causes may include but are not limited to: a. NCI CTCAE Grade 3 or 4 oral mucositis, b. NCI CTCAE Grade 3 or 4 GI disorders [nausea, vomiting, diarrhea, and constipation], c. mechanical obstructions making patient unable to eat, or d. severe depression. 4. Patient undergoing major surgery (central venous access placement and tumor biopsies are not considered major surgery) within 4 weeks prior to randomization. Patient must be well recovered from acute effects of surgery prior to screening. Patient should not have plans to

	undergo major surgical procedures during the treatment period. 5. Patient currently taking androgenic compounds including but not limited to testosterone, testosterone-like agents, oxandrolone, Megestrol acetate, Corticosteroids [for details see Section 5.13.1], Olanzapine [for details see Section 5.13.2], Mirtazapine (however, long-term use of mirtazapine for depression for at least four weeks prior to screening is allowed), Dronabinol, Marijuana (cannabis), or Any other prescription medication or off-label products intended to increase appetite or treat unintentional weight loss*. 6. Patient with pleural effusion requiring thoracentesis, pericardial effusion requiring drainage, edema or evidence of ascites*. 7. 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*. 8. Patient on drugs that may prolong the PR or QRS interval durations, such as any of the antiarrhythmic

	medications Class I (Fast sodium (Na) channel blockers) [Additional details are provided in Section 5.13.2]. 9. Patient unable to readily swallow oral tablets*. 10. Patient with severe gastrointestinal disease (including esophagitis, gastritis, malabsorption). 11. Patient with history of gastrectomy. 12. Patient with uncontrolled diabetes mellitus or unmonitored diabetes mellitus. 13. Patient with cachexia caused by other reasons, as determined by the investigator such as: a. Severe COPD requiring use of home O_2, b. New York Heart Association (NYHA) class III-IV heart failure (see APPENDIX 8), c. AIDS, d. Uncontrolled thyroid disease. 14. Patient receiving strong CYP3A4 inhibitors within 14 days of randomization (see APPENDIX 3). 15. Patient currently receiving tube feedings or parenteral nutrition (either total or partial). 16. Current excessive alcohol or illicit drug use. 17. 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. 18. Enrollment in a previous study with anamorelin HCl 19. Patient actively receiving a concurrent investigational agent, or having received an investigational agent within 28 days of Day 1. All exclusion criteria will be checked at screening visit (Visit 1). *Exclusion Criteria #3, 5, 6, 7g, and 9 are to be re-checked and verified before study drug administration (Visit 2).

Efficacy Assessments	**Primary Efficacy Endpoints:** The co-primary efficacy endpoints are: • Mean change in body weight from baseline over 12 weeks. • Mean change in 5-item Anorexia Symptom Subscale from baseline over 12 weeks. **Secondary Efficacy Endpoints:** • Duration of treatment benefit in weight (≥0) from baseline over 12 weeks. • Duration of treatment benefit in weight (≥ to a predefined threshold) from baseline over 12 weeks. • Duration of treatment benefit in anorexia symptoms (≥0) from baseline over 12 weeks, as measured by the 5-item Anorexia Symptom Subscale. • Duration of treatment benefit in 5-item Anorexia Symptom Subscale (≥ to a predefined threshold) from baseline over 12 weeks. Note: The duration of treatment benefit is measured as the duration for which the patient observed a change from baseline superior or equal to zero, or to the predefined thresholds of clinical meaningfulness, the latter defined through a fully anchor based method using PGIS and PGIC as anchors. • Mean change in FAACT 12-item A/CS domain from baseline over 12 weeks. • Mean change in FACIT-F from baseline over 12 weeks. • Mean change in FAACT total score from baseline over 12 weeks. **Exploratory Efficacy Endpoints:** • Mean change in body weight from baseline up to Week 6, 9, 15, 18, 21, and 24.

	• Mean change in patient-reported anorexia symptom from baseline up to Week 6, 9, 15, 18, 21, and 24 as measured by the 5-item Anorexia Symptom Subscale. • Mean change in FAACT total score from baseline up to Week 6, 9, 15, 18, 21, and 24. • Composite Clinical Response (CCR) at Week 3, 6, 9, 12, 15, 18, 21, and 24. • Change in body weight from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24. • Change in patient-reported anorexia symptoms from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24 as measured by the 5-item Anorexia Symptom Subscale. • Achievement of a clinically meaningful gain in body weight from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24. • Achievement of a clinically meaningful increase in 5-item Anorexia Symptom Subscale from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24. • Percentage of change in body weight from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24. • Changes from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24 in the FAACT (including FAACT total score, FACT-G total score, FAACT TOI, the 12-item A/CS domain and the 4-item Anorexia Concerns Subscale derived from the FAACT). • Changes from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24 in patient-reported fatigue as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) domain as well as the FACIT-F TOI score. • Changes from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24 in the Hunger Assessment Scale. • Changes from baseline to Week 6 and 9 in the Patients' Global Impression of Severity (PGIS) scale and the Patients' Global Impression of Change (PGIC) scale at Week 6 and 9.

Safety Assessments	The following safety assessments will be obtained during the Study: physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), laboratory test (hematology, blood chemistry, urinalysis), adverse events (AEs) assessment, the overall survival on all patients and tumor assessments using CT scan at all sites as per standard local practice.
Stratification	Central randomization will be stratified by line of systemic anti-cancer treatment (first line vs second line vs third line), by type of anti-cancer therapy (immunotherapy vs non-immunotherapy) and by Baseline score of 5-item Anorexia Symptom Subscale (≤10 vs >10).
Statistical Analysis of Efficacy	**Analysis Sets** Statistical analyses will be performed on the following patients' sets: • Intent-to-Treat (ITT): all randomized patients will be analyzed as per planned treatment. • The Full Analysis Set (FAS) includes all randomized patients who take at least one dose of trial medication and for which post randomization data are collected. The definition may be updated at the time of the blind review of the data at the end of the trial. • Per-Protocol (PP): subset of the randomized patients who do not have major protocol violations. • Safety: all patients who receive any study drug and will be analyzed as per actual treatment. **Primary Efficacy Endpoint Hypotheses and Tests** $H_{0w}: MW_a = MW_p$ $H_{1w}: MW_a \neq MW_p$ Where MW_a is the mean change of weight for the anamorelin arm and MW_p is the mean change of weight for the placebo arm. $H_{0a}: MA_a = MA_p$ $H_{1a}: MA_a \neq MA_p$ Where MA_a is the mean change of 5-item Anorexia Symptom Subscale score for the anamorelin arm and MA_p is the mean change of 5-item Anorexia Symptom Subscale score for the placebo arm. The experimental false positive error rate will be preserved because, in order to declare the test component (anamorelin)

	superior to the placebo, both co-primary endpoints must be significant, meaning that both H_{0w} and H_{0a} must be rejected simultaneously. The primary efficacy analyses will be conducted on the ITT. H_{0w} and H_{0a} will be tested using an ANOVA to compare the two treatment groups, at a type-I error threshold of 0.05 two-sided. For each of the imputation the estimate of difference between treatments and its standard error (SE) will be computed, then pooled using the Rubin rule, the pooled difference and the related p-value will be interpreted for the primary efficacy analyses. The mean change effect will be computed as mean of the changes from baseline over 12 weeks by the time of the last assessment (either Week 12 or before, for the analysis at Week 12), and then divided by the number of assessments (observed or imputed) from baseline up to the time of the last assessment (either week 12 or before, in case of death, for the analysis at Week 12). The mean change from baseline over 12 weeks in the secondary efficacy endpoints will be analyzed by means of ANOVA with explanatory variables being the randomized treatment, and the stratification factors. **Sensitivity Analyses** A sensitivity analysis regarding imputation of missing will be performed using data from the placebo group only (control-based imputation) for patients who do not have properly matched patients with complete follow-up. An analysis similar to the primary efficacy analysis will be also conducted after having imputed the values of weight obtained in presence of fluid retention. **Supportive Analyses** Two analyses similar to the primary efficacy analysis will be conducted, one on the FAS population and another one on the PP for each of the primary endpoints. Primary efficacy endpoints will be presented for all the subgroups (listed in Section 9.4.3).

Secondary Efficacy Endpoints Hypotheses and Tests

H_{0d0w}: $D_0Wa = D_0W_p$

H_{1d0w}: $D_0W_a \neq D_0W_p$

Where D_0W_a is the duration of treatment benefit in weight (≥0) for the anamorelin arm and D_0W_p is the duration of benefit in weight for the placebo arm.

H_{0dtw}: $D_tWa = D_tW_p$

H_{1dtw}: $D_tW_a \neq D_tW_p$

Where D_tW_a is the duration of treatment benefit in weight (≥ to a predefined threshold) for the anamorelin arm and D_tW_p is the duration of benefit in weight for the placebo arm.

H_{0d0A}: $D_0Aa = D_0A_p$

H_{1d0A}: $D_0A_a \neq D_0A_p$

Where D_0A_a is the duration of treatment benefit in 5-item Anorexia Symptom Subscale (≥0) for the anamorelin arm and D_0A_p is the duration of benefit in 5-item Anorexia Symptom Subscale for the placebo arm.

H_{0dtA}: $D_tAa = D_tA_p$

H_{1dtA}: $D_tA_a \neq D_tA_p$

Where D_tA_a is the duration of treatment benefit in 5-item Anorexia Symptom Subscale (≥ to a predefined threshold) for the anamorelin arm and D_tA_p is the duration of benefit in 5-item Anorexia Symptom Subscale for the placebo arm.H_{0mf}: $MF_a = MF_p$

H_{1mf}: $MFT_a \neq MF_p$

Where MF_a is the mean change in FAACT 12-item A/CS domain score in the anamorelin arm and MFT_p is the mean change in FAACT 12-item A/CS domain score in the placebo arm. Similar hypothesis systems are set-up for FAACT total score ($H_{0mFt,}$ H_{1mFt}) and FACIT-F ($H_{0mFF,}$ H_{1mFF}).

If the co-primary analysis leads to rejection of H_{0w} and H_{0a}, then the following hypothesis will be tested sequentially: secondary efficacy endpoint related to the duration of treatment benefit in weight (≥0) (H_{0d0w}), the secondary efficacy endpoint related to the duration of treatment benefit in weight (≥ to a predefined threshold) (H_{0dtw}), the secondary

	efficacy endpoint related to the duration of treatment benefit in 5-IASS (≥0) (H_{0d0A}), the secondary efficacy endpoint related to the duration of treatment benefit in 5-IASS ((≥ to a predefined threshold) (H_{0dtA}) and then the secondary efficacy endpoint related to the mean change in FAACT 12-item A/CS domain score (H_{0mF}), FAACT total score and FACIT-F. Each of these tests will be done sequentially at the level of 0.05 bilateral. This hierarchy of testing will allow formal confirmation for the effect on the primary endpoints as well as on the secondary endpoints. This will guarantee the study-wise type-1 error, while not requiring any adjustment for multiple testing. The duration of treatment benefit is measured as the duration for which the patient observed a change from baseline superior or equal to zero, or to the predefined thresholds of clinical meaningfulness. For the purpose of computation, it will be assumed a linear evolution between two measurements. **Exploratory Efficacy Analysis** The duration of benefit and mean change from baseline endpoints will be analyzed like the main analysis for the primary efficacy endpoints or the analyses of the secondary endpoints. All the change from baseline exploratory endpoints except the HAS and the PGIS/C will be analyzed using an ANCOVA model, with explanatory variables being the randomized treatment, the stratification factors and the baseline value. All the responder analyses (CCR and achievement of responder threshold) will be analyzed using a logistic regression, with explanatory variables being the randomized treatment, and the stratification factors. 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.
Statistical Analysis of Safety	All safety and tolerability data will be summarized descriptively.

STUDY FLOW CHART

Study Design and Schedule of Assessments (Screening to Week 9)

Assessment	Screening	Visit Day[14] Treatment Period			
Day	**-7 to -1**	**1**	**22 (+3)**	**43 (+3)**	**64 (+3)**
Week	**-1**	**1**	**3**	**6**	**9**
Visit	**1**	**2**	**3**	**4**	**5**
Informed consent[1]	X				
Medical history	X[13]				
Physical exam[2]	X	X	X	X	X
ECOG PS	X				X
Vital signs	X	X	X	X	X
Height and BMI[3]	X				
Body weight[3]	X	X	X	X	X
12-Lead ECG[4]	X	X	X	X	X
Chemistry/Hematology[5]	X	X	X	X	X
HbA1c	X				
Urine pregnancy[6]	X	X			X
Urinalysis[7]	X				X
Administer FAACT questionnaire 12-item A/CS domain only[8, 9]	X				
Administer FACIT questionnaires (includes all 4 domains, PWB, FWB, SWB, and EWB of FACT-G, 12-item A/CS domain and 13-item FACIT-F fatigue domain) and Hunger Assessment Scale questionnaires [8, 9]		X	X	X	X
Administer PGIS questionnaires for body weight and anorexia[8, 9]	X			X	X
Administer PGIC questionnaires for body weight, anorexia and overall condition[8,9]				X	X
CT scan[10]	X	→	→	→	→
Adverse events[11]	X	X	X	X	X
Prior and concomitant medications (including NSCLC treatment)[12]	X	X	X	X	X
Randomization		X			
Dispense new and/or return blister card for study drug dosing; check compliance		X	X	X	X

[1] Informed consent will be obtained prior to any study-related screening procedures. Procedures may be completed over several visits if desired.

[2] A complete Physical Exam will be conducted and will also focus on evaluation for any signs of pedal edema, pericardial effusion, pleural effusions, and ascites.

[3] Height will be measured in cm. Body weight will be measured in kg using a calibrated scale dedicated for use in this study, and following study-specific procedures as described in APPENDIX .

[4] All patients will have a 12-lead ECG performed in triplicate at 1 hour (±5 minutes) post dose at each visit, with the exception of Screening Visit (where ECG will be taken only pre-dose) and Visit 2, Day 1 (where ECG will be taken also pre-dose). Every effort will be made to perform ECG at the assigned timepoint.

[5] Chemistry and hematology testing will be done under fasting condition. Hematology: CBC with differential count. Chemistry: sodium, potassium, chloride, calcium, total protein, albumin and pre-albumin, AST (SGOT), alkaline phosphatase (ALP), ALT (SGPT), total bilirubin, creatinine, C-reactive protein and glucose.

[6] To be performed for females of childbearing potential within 24 hours prior to the first IMP administration on Day 1. If at the screening visit urine pregnancy test has been done within the 24 hours before the first IMP administration, no urine pregnancy test is to be performed at Visit 2 (Day 1).

[7] Urinalysis will be performed pre-dose and under fasting conditions and will include: Protein, glucose, WBC, erythrocytes, and bacteria.

[8] Patients should complete questionnaires in their native language. Every effort should be made to have the patient complete questionnaires alone. If they cannot physically complete the surveys by themselves, then site personnel may read the questions to the patients and record their answers, and document details of who completed the survey.

[9] Preferred order of the ePRO administration at each visit is based on importance of endpoints: At screening visit FAACT followed by PGIS questionnaires for body weight and anorexia. At Week 1 and Week 3 visits FAACT followed by FACT-G, FACIT-F, and HAS. At Week 6 and Week 9 visits: FAACT, FACT-G, FACIT-F, PGIS questionnaires for body weight and anorexia, PGIC questionnaires for body weight, anorexia and overall condition, and HAS. Of note, the FAACT contains 12 items, and 5 of these items will be used to score the 5-item Anorexia Symptom Subscale and 4 of these items will be used to score the 4-item Anorexia Concerns Subscale (see Section 7.1.2).

[10] All patients will undergo CT scan assessment as per standard local practice for tumor assessment. The baseline tumor assessment may have been obtained within 28 days of the first dose of study drug. Any tumor assessment outside of the screening visit will be assessed and recorded; for details, please see Section 7.2.7.

[11] Adverse events will be collected from Informed consent signature up to the end of the study Week 26 (Visit 11). SAEs must be reported within 24 hours.

[12] Baseline NSCLC treatment regimen will be captured at screening and adherence to this, and all future regimens will be captured throughout the treatment period.

[13] Information on histological or cytological tumor type, genotype and treatment will be collected.

[14] On study days that coincide with chemotherapy administration, all study procedures should be obtained prior to administration of chemotherapy. Patients should arrive for visits prior to dosing, and every effort should be made to have patient blood draws under fasted conditions; fasting status will be documented within the CRF. Patients who withdraw from study prematurely will be requested to complete the Day 64 visit (Week 9) procedures.

Study Design and Schedule of Assessments (Week 12 to 26)

Assessment	Visit Day[9] Treatment Period					Follow-up Period[10] (telephone)
Day	**85 (+3)**	**106 (+3)**	**127 (+3)**	**148(+3)**	**169 (+3)**	**183 (+3)**
Week	**12**	**15**	**18**	**21**	**24**	**26**
Visit	**6**	**7**	**8**	**9**	**10**	**11**
Physical exam[1]	X	X	X	X	X	
Vital signs	X	X	X	X	X	
Body weight[2]	X	X	X	X	X	
12-Lead ECG	X	X	X	X	X	
Chemistry/Hematology[3]	X	X	X	X	X	
HbA1c	X				X	
Urine pregnancy testing (women of childbearing potential only)					X	
Urinalysis[4]					X	
Administer FACIT questionnaires (includes all 4 domains, PWB, FWB, SWB, and EWB of FACT-G, 12-item A/CS domain and 13-item FACIT-F fatigue domain) and Hunger Assessment Scale questionnaires[5]	X	X	X	X	X	
CT scan[6]	X	→	→	→	→	
Adverse events[7]	X	X	X	X	X	X
Concomitant medications (including chemotherapy)[8]	X	X	X	X	X	
Dispense new and/or return blister card for study drug dosing; check compliance	X	X	X	X	End	

1 Physical Exam will focus on evaluation for any signs of pedal edema, pericardial effusion, pleural effusions, and ascites.

2 Body weight will be measured in kg using a calibrated scale dedicated for use in this study and following study-specific procedures as described in APPENDIX 2.

3 All tests will be done under fasting condition. Hematology: CBC with differential count. Chemistry: sodium, potassium, chloride, calcium, total protein, albumin and pre-albumin, AST (SGOT), alkaline phosphatase (ALP), ALT (SGPT), total bilirubin, creatinine, C-reactive protein and glucose.

4 Urinalysis will be performed pre-dose and under fasting conditions and will include: Protein, glucose, WBC, erythrocytes, and bacteria.

5 Patients should complete questionnaires in their native language. Every effort should be made to have the patient complete questionnaires alone. If they cannot physically complete the surveys by themselves, then site personnel may read the questions to the patients and record their answers, and document this. Order of questionnaires should be the 12-item FAACT, FACT-G, FACIT-F, and HAS.

6 All patients will undergo CT scan assessment as per standard local practice for tumor assessment. Any tumor assessment outside of the screening visit will be assessed and recorded (please see Section 7.2.7).

7 Adverse events will be collected from Informed consent signature up to the end of the study Week 26 (Visit 11, follow-up visit). All SAEs must be reported within 24 hours.

8 Adherence to baseline NSCLC treatment regimen and all future regimens will be captured throughout the treatment period.

[9] On study days that coincide with chemotherapy administration, all study procedures should be obtained prior to administration of chemotherapy. Patients should arrive for visits prior to dosing, and patient blood draws under fasted conditions; fasting status will be documented within the CRF. Patients who withdraw prematurely will be requested to complete the Day 183+3 visit (Week 26) procedures.

[10] Follow- up visit on Day 183 +3 (Visit 11) will be conducted by telephone.

LIST OF ABBREVIATIONS

A/CS	12-item Additional Concerns Subscale of the FAACT
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine transaminase (SGPT)
ANC	Absolute Neutrophil Count
AST	Aspartate transaminase (SGOT)
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CBC	Complete Blood Count
CCR	Composite Clinical Response
CI	Confidence interval
CRO	Clinical Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
EC50	half maximal Effective Concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
EGFR	Epidermal Growth Factor Receptor
FAACT	Functional Assessment of Anorexia/Cachexia Treatment
FACIT	Functional Assessment of Chronic Illness Therapy
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-G	Functional Assessment of Cancer Therapy - General

FAS	Full Analysis Set
GCP	Good Clinical Practice
GH	Growth Hormone
GI	Gastrointestinal
H0	Null hypothesis
H1	Alternative hypothesis
HbA1c	Hemoglobin A1c
5-IASS	5-Item Anorexia Symptoms Subscale
IC	Informed Consent
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LBM	Lean Body Mass
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MITT	Modified Intent-to-Treat
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OR	Odds Ratio
PCS	Potentially Clinically Significant
PD-1	Programmed cell death protein 1
PD-L 1	Programmed death-ligand 1
PE	Physical Examination
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PK	Pharmacokinetic

PP	Per protocol
PR	Interval from beginning of the P wave to the beginning of the QRS
Q1	First quartile
Q3	Third quartile
QD	Once Daily
QRS	Duration of QRS complex in the frontal plane
QT	Interval from beginning of the QRS complex to end of the T wave in the frontal plane
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TOI	Trial Outcome Index
ULN	Upper limit of normal
USA	United States of America

1 INTRODUCTION AND RATIONALE

1.1 Background Information

Weight loss and anorexia are among the symptoms that characterize cancer cachexia, a multifactorial syndrome that occurs in more than 80% of patients with cancer before death [Kumar-2010; von Haehling-2010; Aoyagi-2015].

Following the current consensus criteria cancer cachexia is primarily diagnosed either by [Fearon-2011]:

- recent weight loss > 5% over past 6 months (in absence of simple starvation), or

- recent weight loss > 2% and body-mass index (BMI) <20 kg/m^2, or

- sarcopenia.

Reduced food intake in patients with cancer is caused by primary anorexia and can be compounded by secondary nutrition impact symptoms; according to a number of reports, cancer patients describe weight loss and anorexia symptoms as sources of concern/worry, with significant impacts on their daily lives [Hinsley-2007; Hopkinson-2014; McGrath-2002; Hopkinson-2015; Oberholzer-2013].

To better understand the experiences of weight loss/low BMI in lung cancer patients, Helsinn collaborated with PatientsLikeMe [Rodriguez-2017], an online patient network that connects patients and facilitates research. Ninety-five patients participated in an online survey, and 35 of them (36.8%) were classified as having considerable weight loss (defined as ≥ 5% loss of body weight in the past 6 months or ≥ 2% for a BMI less than 20 kg/m^2). Weight loss was found to represent a substantial problem for NSCLC patients, associated with lower quality of life, higher distress level and more severe symptoms (including appetite loss). Patients were also asked to identify which symptoms they experience because of their weight loss had the most significant impact on their life. For these patients the most frequently reported symptoms with significant impacts were changes in food taste (38%), fatigue (38%), and decrease in appetite (33%); early satiety, which is another relevant component of anorexia together with food taste and decreased appetite, was also noted as a symptom having a significant impact in 14% of the patients surveyed [Rodriguez-2017].

Anorexia is a major contributor to the weight loss. Anorexia in cancer may be characterized as a general loss of appetite, early satiety, altered food preferences, or a combination of these [Molfino-2015]. Cancer related anorexia is also a major clinical problem and adversely influences nutritional status in advanced cancer [Yavuzsen-2005] and has been associated with poorer survival in multiple studies [Montazeri-2009; Sundstrøm-2006; Fielding-2007; McKernan-2008; Collette2004Yeo-2006; Sullivan-2006]. Anorexia is the second most common symptom after fatigue in patients with advanced cancer [Lis-2009]. In a study conducted by Sundstrom et al. appetite loss emerged as the most significant independent indicator for survival in advanced NSCLC patients and concluded that assessment of anorexia, including appetite loss is a valuable tool in determining thoracic radiotherapy strategy [Sundstrøm-2006].

Reduced dose intensity of chemotherapy and increased toxicity have been noted in patients with weight loss, which can be of sufficient severity to require dose reductions, treatment delays or definitive termination of treatment, such that weight-losing patients do not achieve the full potential benefit of their cancer therapy [Ross -2004; Andreyev-1998]. Furthermore, in a study in advanced NSCLC patients comparing non-weight losing patients to weight losing/underweight patients (≥5% weight loss in prior 6 months or >2% weight loss with BMI<20 kg/m^2), it was found that all patient-reported outcome (PRO) measures (FACT-G and specific domains from FAACT, FACIT-F, FACIT-L) and performance status (Karnofsky PS and ECOG) were worse in the weight losing/underweight patients compared to non-weight losing patients, and that while all these measures declined over a 6 month period, the rate of decline was more rapid in the weight-losing/underweight group [LeBlanc-2015].

In summary, weight loss, along with anorexia (including appetite loss), are common, debilitating, and concerning occurrences for advanced cancer patients. Despite the high prevalence and the association with poor prognosis, there has been a lack of therapeutic advance in managing these symptoms of advanced cancer patients, and pharmacological interventions remain limited.

Therefore, the treatment of malignancy associated weight loss and anorexia in cancer patients are an area of unmet medical need.

Anamorelin HCl is an orally-active selective ghrelin receptor agonist. Ghrelin is the endogenous ligand for the G-protein-coupled ghrelin receptor, GRLN (formerly known as the growth hormone [GH] secretagogue receptor, GHS-R) [Kojima-1999]. It is synthesized predominantly in the stomach and has a short circulating half-life (~15 minutes) in both animals and humans, which limits its therapeutic potential since long-term efficacy would necessitate continuous infusion. Nevertheless, research into the effects of ghrelin or longer-acting ghrelin mimetics has revealed that ghrelin possesses anabolic, appetite-enhancing, adiposity-increasing, and anti-inflammatory properties [Guillory-2013]; along with GI-prokinetic activity [Trudel-2002].

In vitro, anamorelin displays high affinity and selective binding to the ghrelin receptor and is a highly potent GH secretagogue by *in vitro* assay (EC50 = 1.5 nM). *In vivo*, anamorelin HCl elicited a robust GH release following oral administration to dogs and a potent appetite enhancing effect in rats following intracerebral administration; increases in food intake and body weight were also noted in animal models [Trudel-2002]. In clinical studies, anamorelin treatment is also associated with increases in appetite and body weight, along with gains in lean body mass (LBM) and improvements in health-related QoL measures [Temel-2016; Currow-2014].

1.2 Anamorelin: preclinical and clinical data

1.2.1 Preclinical 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 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. 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.

A detailed description of the preclinical data available is provided in the relevant sections of the Investigator's Brochure.

1.2.2 Phase 1 Clinical Data

Anamorelin HCl has been studied in 12 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. Anamorelin HCl increased GH, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 and produced the desired biologic effects of significant appetite stimulation, increase of food intake, body weight gain. The threshold dose 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. 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, diarrhea, visual focus impairment, and dizziness. The primary adverse events of special interest from the Phase 1 studies included increases in serum transaminases and electrocardiogram (ECG) abnormalities including transient PR, QRS and QT prolongations at the supratherapeutic doses of 300 and 400 mg (based on 24-hour Holter monitoring data from Study HT-ANAM-112). Of note, none of the QTcF absolute values were above 450 ms. The PR, QRS and QT increases were considered not clinically significant by the Investigator. To better assess the ECG effects of anamorelin HCl, a thorough QT/QTc study (Study HT-ANAM-113) was then conducted, and the overall results showed that anamorelin had no meaningful effect on ventricular repolarization.

1.3 Other Clinical Data

Anamorelin HCl was additionally evaluated in one Phase 2 program (including four studies), and in one Phase 3 program (including two studies) where 361 and 972 patients, respectively, were treated for a total of 915 patients with cancer treated with anamorelin HCl.

Phase 2 program consisted of studies RC-1291-203/205 and RC-1291-206 which evaluated a total of 135 patients with a variety of tumor types and weight loss, while the fourth Phase 2 study- Study ST-ANAM-207 included 226 patients with NSCLC and randomized patients 1:1:1 to placebo, anamorelin HCl 50 mg, or anamorelin HCl 100 mg.

The Phase 2 program demonstrated that anamorelin HCl significantly increased LBM and body weight. Treatment with anamorelin HCl at dose levels of 50 mg and 100 mg QD for up to 12 weeks was generally well tolerated. No dose limiting toxicity was observed.

The Phase 3 ROMANA program consisted of two studies (HT-ANAM-301 and HT-ANAM-302) and an associated safety extension study (HT-ANAM-303) and together evaluated a total of 972 NSCLC patients for up to 24 weeks.

Results from HT-ANAM-301 and HT-ANAM-302 demonstrated that patients assigned to anamorelin experienced an increase in lean body mass, body weight and improvement in their anorexia/cachexia symptoms compared to those assigned to placebo in both the studies, but no difference in handgrip strength was observed.

In a Phase 3, multicenter, open-label, uncontrolled non-Helsinn sponsored clinical study conducted in Japan (ONO-7643-05), at a dose level of 100 mg QD of anamorelin for 12 weeks, the proportion of patients with cancer cachexia who maintained or gained lean body mass was 63.3% (31/49 subjects). Moreover, patients experienced an increase in body weight, improved appetite, stimulated protein synthesis, as measured by biomarkers IGF-1 and IGFBP-3, and improved the nutritional status, as measured by prealbumin.

In another Phase 3 multicenter, open-label, uncontrolled non-Helsinn sponsored clinical study conducted in Japan (ONO-7643-06), at a dose level of 100 mg QD of anamorelin for 24 weeks, the increase in body weight and the improved appetite in patients with cancer cachexia were confirmed, and its efficacy was maintained throughout the 24-week treatment period.

Safety results from Phase 3 ROMANA program indicated that anamorelin HCl was well tolerated.

A positive safety profile was also confirmed in studies ONO-7643-05 and ONO-7643-06; although there was a high incidence of adverse drug reactions related to the increased blood glucose and cardiac function, no event was indicative of a significant risk.

Additional information on currently available clinical data is provided in the relevant sections of the Investigator's Brochure.

The primary purpose of the present ANAM-17-20 study is to further evaluate the impact of anamorelin HCl on body weight and anorexia symptoms in patients with advanced non-small cell lung cancer (NSCLC).

1.4 Study Rationale

1.4.1 Rationale for Study Population

This study will be conducted in adult patients with advanced NSCLC. Patients with NSCLC are being chosen for investigation because of the prevalence of weight loss and anorexia and the prognostic implications of weight loss for these patients including reduced quality of life and increased symptom burden, as well as shortened survival.

Among patients with NSCLC, those with BMI < 20 kg/m^2 represent a more malnourished/at-risk population, which therefore has a more pressing need for an effective

therapy to address weight loss and anorexia symptoms. Therefore ANAM-17-20 will enroll only patients with BMI < 20 kg/m^2 and will also require >2% weight loss over the past 6 months to better align with the consensus definition of anorexia-cachexia [Fearon-2011]. In addition, as this study is investigating improvements in anorexia symptoms, patients enrolled must also demonstrate ongoing problems with their appetite/eating.

1.4.2 Rationale for Study Protocol and Design

Helsinn is proposing to target weight loss and anorexia in cancer cachectic patients, as these two conditions are rated amongst the top concerns of these advanced stage patients and there are currently limited treatment options. This study will be an adequate and well-controlled study designed to demonstrate superiority of anamorelin HCl vs placebo on the gain in body weight and improvement in anorexia symptoms.

A total of 316 patients with advanced NSCLC with cachexia will be randomized 1:1 to anamorelin HCl 100 mg or placebo, taken orally once daily for a total of 24 weeks.

In this study, the primary and secondary efficacy analysis will be conducted at 12 weeks. Additional exploratory efficacy and safety analyses will also be conducted at 24 weeks in order to collect data over longer treatment duration.

1.4.3 Rationale 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 (HT-ANAM-301 and HT-ANAM-302) in NSCLC patients 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 patients with NSCLC-C was also observed. In the safety extension study (HT-ANAM-303), whereby patients from Studies HT-ANAM-301/302 continued dosing for up to an additional 12 weeks, a 100 mg dose level was also well tolerated, with no new safety signals identified in the longer dosing period.

Due to the lack of safe and effective treatments for weight loss and anorexia in cancer patients with cachexia, placebo treatment will be used in the control group in this study.

1.5 Rationale for protocol amendment

Further to FDA advice obtained on the primary endpoints analysis, the Sponsor redefined the primary efficacy endpoints to duration of treatment benefit from baseline to Week 12 for body weight and anorexia (5-IASS). Based on this new approach a redefinition of the secondary and exploratory endpoints was also included. Such changes were implemented in protocol v4.0 dated 22 Mar 2021 and 4.A dated 03 Sep 2021.

However, during the course of the study, an error was discovered in the algorithm used to determine the statistical power for the evaluation of the duration of treatment benefit from baseline to Week 12 for body weight and anorexia (5-IASS) co-primary endpoints.

Corrected calculations revealed that each trial, with the current planned sample size of 316 patients, would be underpowered for the 5-IASS endpoint. Indeed, new simulations correcting for the programming error were performed and these results confirmed high

power (over 98%) for the weight-based co-primary endpoint but showed low power for the 5-IASS co-primary endpoint (between 60% and 70%).

Based on corrected simulations and calculations, obtaining an acceptable power would require to at least double the sample size.

At the current stage of the studies, such a huge change in sample size would be of great impact for cachectic cancer patients who are looking at anamorelin as the only promising investigational agent in development for treating the two important unmet needs of malignancy associated weight loss and anorexia and hoping in its prompt approval.

The Sponsor endorses the importance of having two adequate and well controlled trials, each achieving statistical significance. To achieve a proper power for the analysis of the 5-IASS co-primary endpoint, the Sponsor will perform the analysis by adopting same methodological approach and same variables, i.e., two co-primary endpoints still keeping body weight and 5-IASS as efficacy variables, but measuring the mean change from baseline in replacement of the duration of treatment benefit, as defined based on scientific and clinical experts' feedback and confirmed as a feasible endpoint by sample size calculations.

2 STUDY OBJECTIVES

2.1 Primary Objective

To demonstrate superiority of anamorelin HCl vs placebo on the gain in body weight and improvement in anorexia symptoms.

2.1.1 Estimand

The analysis to address this objective has been developed in consideration of ICH Topic E9(R1) Statistical Principles for Clinical Trials: Note for Guidance on Statistical Principles in Clinical Trials [ICH-1998]. Specifically, we have anticipated two intercurrent events: study drug discontinuation and death. We consider appropriate to assess a treatment effect "regardless of" whether patients continue with treatment or not. Therefore, we will implement a treatment policy estimand. Efforts will be made to retain all patients in study follow-up whether they have discontinued the study treatment or not. The method of data imputation will take into account that patients have discontinued study treatment. Deaths likely will be due to underlying disease. The aim of anamorelin treatment is to increase body weight and improve anorexia symptoms while the patient is alive. Hence, it is necessary and sufficient to obtain regular assessments on body weight and anorexia symptoms between randomization and death.

2.2 Secondary Objectives

To evaluate the safety and tolerability of anamorelin HCl, and to further evaluate anamorelin efficacy profile.

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoint

The co-primary efficacy endpoints are:

- Mean change in body weight from baseline over 12 weeks.
- Mean change in 5-item Anorexia Symptom Subscale from baseline over 12 weeks.

3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Duration of treatment benefit in weight (≥0) from baseline over 12 weeks.
- Duration of treatment benefit in weight (≥ to a predefined threshold) from baseline over 12 weeks.
- Duration of treatment benefit in anorexia symptoms (≥0) from baseline over 12 weeks, as measured by the 5-item Anorexia Symptom Subscale.
- Duration of treatment benefit in 5-item Anorexia Symptom Subscale (≥ to a predefined threshold) from baseline over 12 weeks.

The duration of treatment benefit is measured as the duration for which the patient observed a change from baseline superior or equal to zero, or to the predefined thresholds of clinical meaningfulness, the latter defined through a fully anchor based method using PGIS and PGIC as anchors.

- Mean change in FAACT 12-item A/CS domain from baseline over 12 weeks.
- Mean change in FACIT-F from baseline over 12 weeks.
- Mean change in FAACT total score from baseline over 12 weeks.

3.1.3 Exploratory Efficacy Endpoints

- Mean change in body weight from baseline up to Week 6, 9, 15, 18, 21, and 24.
- Mean change in patient-reported anorexia symptoms from baseline up to Week 6, 9, 15, 18, 21, and 24, as measured by the 5 item Anorexia Symptom Subscale.
- Mean change in FAACT total score from baseline up to Week 6, 9, 15, 18, 21, and 24.
- Composite Clinical Response (CCR) at Week 3, 6, 9, 12, 15, 18, 21, and 24.
- Change in body weight from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24.
- Change in patient-reported anorexia symptoms from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24 as measured by the 5-item Anorexia Symptom Subscale.

- Achievement of a clinically meaningful gain in body weight from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24.
- Achievement of a clinically meaningful increase in 5-item Anorexia Symptom Subscale from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24.
- Percentage of change in body weight from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24.
- Changes from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24 in the FAACT (including FAACT total score, FACT-G total score, FAACT TOI, the 12-item A/CS domain and the 4-item Anorexia Concerns Subscale derived from the FAACT).
- Changes from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24 in patient-reported fatigue as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) domain as well as the FACIT-F TOI score.
- Changes from baseline to Week 3, 6, 9, 12, 15, 18, 21, and 24 in the Hunger Assessment Scale.
- Changes from baseline to Week 6 and 9 in the Patients' Global Impression of Severity (PGIS) scale and the Patients' Global Impression of Change (PGIC) scale at Week 6 and 9.

3.2 Safety Assessments

The following safety assessments will be performed: physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), laboratory test (hematology, blood chemistry, urinalysis), adverse events (AEs) assessment, tumor assessment using CT scan and the overall survival on all patients.

Overall Survival

- Overall survival up to the end of study (i.e., week 26, follow-up visit).

Tumor Assessments

- Change in tumor assessment (overall response categorized into complete response, partial response, stable disease and progressive disease) using CT scans at all sites as per standard local practice. For additional information please refer to Section 7.2.7.

4 STUDY PLAN

4.1 Study Design

The study is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of anamorelin HCl. Approximately 316 patients with advanced NSCLC with cachexia will be randomized 1:1 to anamorelin HCl 100 mg or placebo, taken orally once daily (QD) for a total of 24 weeks. Patients will be instructed to take the study drug at least 1 hour before their first meal of the day.

Central randomization will be stratified by line of systemic anti-cancer treatment (first line vs second line vs third line), by type of anti-cancer therapy (immunotherapy vs non-immunotherapy) and by Baseline score of 5-item Anorexia Symptom Subscale (≤10 vs >10). Patients will visit the site every 3 weeks for the study duration of 24 weeks. A follow-up telephone visit is scheduled at Week 26.

Regarding Patients that never received anticancer treatment prior to enter the study, still qualifying to participate following full compliance to eligibility criteria, will be eligible to enter the study and will be allocated to first line treatment in IWRS.

4.2 Study Duration

Each patient will stay on study for a maximum of 27 Weeks (including 1 week screening period and 2 weeks follow-up period).

Total number of visits per patient: 10 visits plus 1 telephone contact for follow-up visit.

The study will be approximately 27 Weeks in duration including the following:

- A screening period from Day -7 to -1 (on-site Visit 1)
- A 24-week treatment period (on-site Visit 2 to Visit 10)
- A 2-week follow-up period (telephone Visit 11)

A patient will be defined as having completed the Study if patient completes the follow-up visit (Visit 11).

The overall study completion date is defined as the date of last patient's last visit or telephone contact.

4.3 Study population

4.3.1 Number of Subjects

A total of 316 patients with advanced NSCLC with cachexia will be randomized 1:1 to anamorelin HCl 100 mg or placebo (158 patients per treatment arm).

4.3.2 Inclusion Criteria

1. Signed written informed consent.
2. Female or male ≥18 years of age.

3. Documented histologic or cytologic diagnosis of American Joint Committee on Cancer (AJCC) Stage III or IV NSCLC. Stage III patient must have unresectable disease.
4. Body mass index < 20 kg/m2 with involuntary weight loss of >2% within 6 months prior to screening.
5. Ongoing problems with appetite/eating associated with the underlying cancer, as determined by having score of ≤ 17 points on the 5-item Anorexia Symptom Scale and ≤ 37 points on the 12-item FAACT A/CS.
6. Patient receiving or not receiving systemic anti-cancer treatment at the time of screening are eligible to participate. Systemic anti-cancer treatment includes first, second, third treatment line with chemotherapy/radiation therapy, immunotherapy or targeted therapy.

   Patient not receiving anti-cancer treatment is eligible if:

   a. Not planning to receive anti-cancer treatment and/or at least 14 days must be elapsed from the completion of prior treatment at the day of screening, in case underwent previous cycle,

   OR

   b. Planning to receive anti-cancer treatment within 14 days from randomization and/or at least 14 days must be elapsed from the completion of prior treatment at the day of screening, in case underwent previous cycle,

   OR

   c. Patient on palliative care treatment.
7. ECOG performance status 0, 1 or 2 at screening (see protocol APPENDIX 1)
8. AST (SGOT) and ALT (SGPT) ≤ 3 x ULN or if hepatic metastases are present ≤ 5 x ULN.
9. Adequate renal function, defined as creatinine ≤2 × ULN, or calculated creatinine clearance >30 ml/minute.
10. Female patient shall be: a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having a negative urine pregnancy test within 24 hours prior to dose of investigational product*
    Notes:
    a) Female patient of non-childbearing potential is defined as being in post-menopausal state since at least 1 year; or having documented surgical sterilization or hysterectomy at least 3 months before study participation.

    b) Reliable contraceptive measures include implants, injectables, combined oral contraceptives, intrauterine devices, vasectomized partner or complete (long term) sexual abstinence.
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 1).

*Inclusion criterion #10 will be re-checked and verified at Day 1 (Visit 2).

4.3.3 Exclusion Criteria

1. Patient with other forms of lung cancer (e.g., small cell, neuroendocrine tumors).
2. Woman who is pregnant or breast-feeding.
3. Reversible causes of reduced food intake, as determined by the Investigator*. These causes may include, but are not limited to:
   a. NCI CTCAE Grade 3 or 4 oral mucositis,
   b. NCI CTCAE Grade 3 or 4 GI disorders [nausea, vomiting, diarrhea, and constipation],
   c. mechanical obstructions making patient unable to eat, or
   d. severe depression.
4. Patient undergoing major surgery (central venous access placement and tumor biopsies are not considered major surgery) within 4 weeks prior to randomization. Patient must be well recovered from acute effects of surgery prior to screening. Patient should not have plans to undergo major surgical procedures during the treatment period.
5. Patient currently taking androgenic compounds including but not limited to testosterone, testosterone-like agents, oxandrolone;

   Megestrol acetate;

   Corticosteroids [for details see Section 5.13.1];

   Olanzapine, mirtazapine (however, long-term use of mirtazapine for depression for at least four weeks prior to screening is allowed);

   Dronabinol;

   Marijuana (cannabis), or

   Any other prescription medication or off-label products intended to increase appetite or treat unintentional weight loss*
6. Patient with pleural effusion requiring thoracentesis, pericardial effusion requiring drainage, edema or evidence of ascites*
7. 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.*

8. Patient on drugs that may prolong the PR or QRS interval durations, such as any of the antiarrhythmic medications Class I (Fast sodium (Na) channel blockers)
9. Patient unable to readily swallow oral tablets*.
10. Patient with severe gastrointestinal disease (including esophagitis, gastritis, malabsorption).
11. Patient with history of gastrectomy.
12. Patient with uncontrolled diabetes mellitus or unmonitored diabetes mellitus.
13. Patient with cachexia caused by other reasons, as determined by the investigator such as:
    a. Severe COPD requiring use of home O_2,
    b. New York Heart Association (NYHA) class III-IV heart failure
    c. AIDS
    d. Uncontrolled thyroid disease.
14. Patient receiving strong CYP3A4 inhibitors within 14 days of randomization (see APPENDIX 3)
15. Patient currently receiving tube feedings or parenteral nutrition (either total or partial).
16. Current excessive alcohol or illicit drug use.
17. 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.
18. Enrollment in a previous study with anamorelin HCl.
19. Patient actively receiving a concurrent investigational agent or having received an investigational agent within 28 days of Day 1.

All Exclusion Criteria should be checked at the day of screening visit (Visit 1).

*Exclusion Criteria #3, 5, 6, 7g, and 9 are to be re-checked and verified before study drug administration (Visit 2).

5 STUDY DRUG MANAGEMENT

5.1 Description of Study Treatments

Investigational product

Name:	**Anamorelin HCl**
Dosage form:	Tablets
Strength:	100 mg
Dosing	At least 1 hour before the first meal of the day
Route of administration:	Oral

Placebo

Name:	Placebo to match 100 mg tablets
Dosage form:	Tablets
Strength:	N/A
Dosing:	At least 1 hour before the first meal of the day
Route of administration:	Oral

5.2 Treatment Groups

Group 1 / Test group – 100 mg anamorelin HCl

Group 2 / Control group – Placebo

5.3 Dose and Administration

Investigational product: Anamorelin HCl

Patients will take 1 tablet on Day 1 and daily thereafter. Patients will be supplied with study drug at visit 2 and re supplied at Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), Visit 7 (Week 15), Visit 8 (Week 18) and Visit 9 (Week 21). 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.

5.4 Packaging, Labelling and Shipment

Study drug will be primary packed in the form of blisters; this will be secondary packed in form of carton wallet cards. Each wallet card will contain either 100 mg anamorelin HCl tablets or matching placebo tablets. The amount of tablets to be used for a single 3-weeks cycle of treatment will be included in the wallet card, that will be labelled with individual kit number for identification.

5.5 Storage

An exact inventory of all study kits must be maintained at the investigational site. The study kits 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).

5.6 Drug Depots

The study kits will be shipped to clinical sites either from central depot, or from local drug depots as applicable for further distribution to sites. Study kits shipments to the investigational sites are triggered via the IWRS.

5.7 Accountability

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

Used study kits will undergo drug accountability performed by the study monitor during the course of the study.

Following drug accountability, used study kits are to be retained at the site until study end. Used and unused study kits remaining at sites at the end of the study will be returned to the drug depots for destruction.

In case the site is strictly required by local regulation not to retain used study kits, site is authorized to destroy them locally, following site destruction procedure, only after accountability done and authorization provided by Sponsor.

A detailed description of study drug handling will be provided in Study Drug Manual.

5.8 Administration of Study Treatment

At Day 1 (Visit 2), after confirming patient's eligibility, the Investigator or designee will get connected to the IWRS to randomize the patient. An IWRS will be employed for the randomization activities taking into account the stratification factors (See Section 9.1). The IWRS will assign a study kit number to the patient and the Investigator (or Investigator's designee) will receive the IWRS notification mentioning the study kit number assigned to the patient for which the request was made. The hospital pharmacist, or designated responsible person, will select from the study kits stored at the site pharmacy the corresponding kit as indicated by the IWRS and fill-in the blank space(s) on the outer study kit label with the patient's identification number which was assigned by IWRS during screening.

Allocation and distribution of the study kit to the Investigator or Investigator's designee is tracked by attaching the study kit label peel-off portion onto the study site drug accountability log (or similar document).

Adequate written instructions (in form of a Study Drug Manual) for use for the pharmacist or designated person will be provided to him/her for the management of the study kit at each study site.

The relevant labels on the study kits will be filled in according to the provided instructions.

Patients will take 1 tablet on Day 1 (if a fasting state is not possible on Day 1, the patient will start study drug on Day 2) and daily thereafter. Patients will be supplied with study drug at Visit 2 and resupplied at Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), Visit 7 (Week 15), Visit 8 (Week 18) and Visit 9 (Week 21).

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.

5.9 Blinding

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

As far as possible, without compromising patient safety the Investigator may discuss the case with the medical monitor prior to breaking the blind. The Investigator has in any case unrestricted and immediate access to break the treatment code, and irrespective of the medical monitor's advice. If the treatment code is broken, the Investigator(s) must document and report it to Sponsor within 24 hours.

Any unblinding of the study treatment will be performed by IWRS (24-hour 7-day coverage). If the code is broken by the Investigator, the patient should be discontinued from the study drug, but every effort will be made to collect data from the protocol-specified assessments as detailed in Section 6.3. The unblinding procedure will be detailed in the IWRS manual that will be provided separately to the Investigator.

The Drug safety officer may proceed to unblinding. The unblinding procedure will be managed through the IWRS. The patient will not be discontinued from the study treatment. No notification of unblinding will be disclosed.

5.10 Treatment Assignment and Randomization - Use of IWRS

Randomization will be used to avoid bias in assigning treatments to patients. 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.

The 5-item Anorexia Symptom Subscale score will be read from electronic diary then entered into the IWRS.

Central randomization in a double-blind manner will stratify patients using strata defined in Section 9.1.

5.11 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.

5.12 Occupational safety

No studies have been performed on the ability to drive vehicles and operate machinery.

5.13 Prior and concomitant medications

Concomitant medications must be recorded from 14 days prior to the first dose of study drug through the last dose of study drug.

Use of diuretics and changes in diuretics use will be collected and recorded at each visit.

Prophylactic infusion of saline or other hydration solutions prior to or after chemotherapy in order to prevent toxic reactions related to chemotherapy is to be recorded on the appropriate eCRF page; this should also include rehydration events that occur outside of the clinical site.

Infusion of blood products is to be recorded.

All medications administered in relation to diagnostic procedures, e.g., anesthetics and antibiotics are not to be recorded.

5.13.1 Use of corticosteroids

Corticosteroids are permitted for a maximum of 5 consecutive days per each chemotherapy and/or radiation cycle if administered as co-medication in chemotherapy and/or radiotherapy protocols and for any use other than "appetite stimulant".

As well, even single intake of corticosteroids to increase appetite or treat unintentional weight loss is not permitted.

Inhaled steroids for respiratory disorders and topical steroids for skin disease are allowed at any time.

5.13.2 Prohibited Medications

The primary CYP isoforms responsible for the metabolism of anamorelin HCl are CYP3A4 and CYP2D6. Cytochrome P450 in vitro inhibition testing demonstrated modest inhibitory effects against CYP3A4 and no inhibitory effects against CYP2D6. The use of strong CYP3A4 inhibitors is an exclusion criterion and drugs known to strongly inhibit CYP3A4 (ketoconazole, clarithromycin, itraconazole, nefazodone, telithromycin) should be avoided two weeks prior to study entry and throughout the trial. If a patient is required to take a strong CYP3A4 inhibitor while enrolled in this trial, then anamorelin dosing must be discontinued. Although moderate or weak CYP3A4 inhibitors may be used, they should be avoided when possible. Verapamil although listed as moderate CYP3A4 inhibitor (see APPENDIX 3), is not allowed at any time during the course of the study as may prolong PR intervals. 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. See APPENDIX 3.

Systematic long-term application of topical lidocaine preparations is allowed. Drugs that may prolong the PR or QRS interval durations, such as any of the antiarrhythmic

medications Class I (Fast sodium (Na) channel blockers) are prohibited for the study duration.

The use of beta-blockers agents to control hypertension could be allowed only for those drugs that do not interfere with PR and QRS interval; sotalol, being classified as class III antiarrhythmic agent and also as beta-blocker, is to be avoided [Yap-2003]. Other beta-blockers, like nebivolol or metoprolol, could be allowed if hypertension is controlled before entering the study.

Patients should not take any prescription medication or off-label products intended to increase appetite or treat unintentional weight loss during the study; these include, but are not limited to, androgenic compounds (including but not limited to testosterone, testosterone-like agents, oxandrolone), megestrol acetate, corticosteroids (please see Section 5.13.1 for regulation regarding use of corticosteroids), dronabinol or marijuana (cannabis).

The recently released version of NCCN guidelines [NCCN guidelines on antiemesis version 2.2020] for CINV prophylaxis has introduced the possibility to use olanzapine as part of the antiemetic regimen; the recommended dose is 5-10 mg on day 1-4 as used in the phase 2-3 trials [Navari-2016]. Although weight gain has been reported as side effect of olanzapine in psychiatric settings trials [Allison-2001], it has not been observed in oncology trials and, consequently, its use as part of the CINV prophylaxis is admitted.

Based on the above, the use of olanzapine is accepted providing that the investigators adhere to the NCCN recommendations with special regard to dose and schedule of administration.

Use of mirtazapine is also prohibited, however, mirtazapine is allowed if taken for depression and for at least 4 weeks prior to screening.

Patients should not be on treatment with methylphenidate; tube feeding at the time of the study start and during the study is forbidden.

5.13.3 Concurrent NSCLC Treatment

Depending on the genetic variant and on the treatments' lines, anti-cancer treatment for type and stage of NSCLC, proposed anticancer treatment includes the use of platinum- and non- platinum- based chemotherapy, immune checkpoint inhibitors therapy and targeted therapy as per NCCN guidelines [NCCN-2018].

Details on the allowed treatments are listed below:

1. Patients on chemotherapy and/or radiation therapy
    - This includes patients initiating/planning to initiate chemotherapy and/or radiation therapy within ±14 days of randomization.

- This also includes patients receiving maintenance chemotherapy. For these patients, they should continue maintenance chemotherapy as indicated during the study.
- For all patients receiving chemotherapy, if study visits coincide with chemotherapy administration, all study procedures should be performed prior to administration of chemotherapy.

2. Patients on immunotherapy
   - This includes patients initiating/planning to initiate PD-1/PD-L 1 inhibitor regimens within ±14 days of randomization.
3. Patients on Targeted therapy
   - This includes patients initiating/planning to initiate targeted therapy regimens within ±14 days of randomization.
4. Patients currently not taking any treatment for their NSCLC
   - This includes patients on palliative care treatment.

If the primary treatment for NSCLC is changed, interrupted, or permanently discontinued during the planned duration of this trial, therapy with anamorelin HCl or placebo will continue until completion of this study.

Treatment with all chemotherapeutic and targeted agents should be given in accordance with the manufacturer's warnings and directions and recorded as concomitant medication. Treatment for NSCLC should not be held or delayed in order to begin this trial.

5.13.4 Use of contraceptive measures

Female patient of childbearing potential or male patients of fathering potential shall use reliable contraceptive measures for the whole duration of the study and until Visit 11 (Week 26). Reliable contraceptive measures include implants, injectables, combined oral contraceptives, intrauterine devices, vasectomized partner, condoms, spermicide or complete (long term) sexual abstinence.

5.14 Rescue Medication

Not applicable.

5.15 Treatment Compliance

Patients will be instructed to bring all blister cards to each study visit during the treatment period for a compliance/accountability check. A patient will be considered to be compliant with therapy if s/he takes all study drugs provided. Compliance will be defined overall.

6 STUDY CONDUCT

6.1 Study Procedures by Time Point

6.1.1 Visit 1 (Screening, Day -7 to Day -1)

If the Investigator considers a patient to be potentially eligible for the study, written informed consent for participation in the study must be obtained before any study-related procedures starts. The patient will be screened within 7 days prior to randomization (Day 1) and study drug administration; the following procedures will be performed, and data collected during this visit for eligibility purposes:

- Informed consent.
- Significant medical history.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); Results of this PE will be inserted in source data and in the relevant pages of eCRF.
- ECOG Performance Status.
- Vital signs (including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Body weight, height and BMI.
- Prior body weight loss will be verified by the use of patient medical charts; this information can be retrieved either by hospital or family doctor medical charts.
- 12-Lead ECG, in triplicate.
- Chemistry and hematology testing, including HbA1c under fasting conditions.
- Urine pregnancy test for females of childbearing potential.
- Urinalysis under fasting status.
- Administration of FAACT 12-item A/CS domain and PGIS questionnaires for body weight and anorexia.
- CT scan for tumor assessment. The baseline tumor assessment may have been obtained within 28 days of the first dose of study drug (see Section 7.2.7).
- AEs will be collected from the Informed consent signature up to Follow-up visit.
- Prior and concomitant medications data will be collected.

Based on the relevant above mentioned assessments outcome, the Investigator will decide if the patient is eligible for the study. If eligible, patient will be reminded to come back to clinical site under fasting condition for Visit 2 for laboratory assessments and to be administered with study drug.

6.1.2 Visit 2 (Randomization/Treatment Period, Day 1): Week 1

Patient will arrive at the clinical site under fasting condition. Once at the site, Investigator or designated personnel will re-check the following criteria:

- inclusion criterion # 10 (Urine pregnancy test) and
- exclusion criteria # 3, 5, 6, 7g, 9.

If patient is confirmed eligible, authorized study personnel will proceed with randomization procedures. The IWRS will provide the study kit number to be dispensed to the patient **only after** all the following pre-dose assessments are completed for baseline measurements:

- Laboratory assessments, including:
  - Chemistry,
  - Hematology.
- Body weight via scale measurement, to be done prior to study drug administration.
- 12-Lead ECG pre dose, in triplicate.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); results of this PE will be inserted in source data and in the relevant pages of eCRF.
- Vital signs (including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Adverse events recording.
- Prior and concomitant medications (not including NSCLC treatment) recording.
- Administration and completion of:
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB of FACT-G, 12-item A/CS domain and 13-item FACIT-F fatigue domain),
  - Hunger Assessment Scale questionnaire.
- Once completed these pre-dose assessments the patient will be “randomized” and new study kit will be dispensed.
- CT scan for tumor assessment. The baseline tumor assessment may have been obtained within 28 days prior the first dose of study drug (see Section 7.2.7).
- Study drug will therefore be administered. The date and the precise time (hh:mm) of the study drug must be recorded in the source records as well as on the relevant eCRF page.
- One hour post study drug administration patient will undergo ECG measurement in triplicate.

- NSCLC treatment regimen will be collected at Baseline and any dose adjustments, as and if applicable.
- Before leaving the clinic, the patient will be reminded about the prohibited concomitant medications (see Section 5.13.2 for details).
- Patient will also be reminded to come back to clinical site in 3 weeks for next visit and be reminded to arrive at the hospital under fasting conditions.

6.1.3 Visit 3 (Day 22+3): Week 3

The patient will return to the trial site on Visit 3, at Day 22 (+3), approximately 3 weeks after Visit 2. Patient will arrive at the hospital under fasting conditions.

The patient will undergo the following procedures/assessments:

- Study drug administration.
- Laboratory assessments, including:
  - Chemistry,
  - Hematology.
- Vital signs including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Body weight via scale measurement, to be done prior to study drug administration.
- A dedicated physical examination with focus to monitoring the signs and symptoms of edema (see Section 7.2.2.1 for details); results of this PE will be inserted in source data and in the relevant pages of eCRF.
- 12-Lead ECG (1 hour post dose), in triplicate.
- Adverse Events, procedures, and hospitalizations assessment.
- Administration and completion of
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB domains of FACT-G, 12-item A/CS domain and FACIT-F fatigue domain),
  - Hunger Assessment questionnaire.

Questionnaires will be administered in the order presented here and administered from 1 to 4 hours post study drug administration.

- CT scan may be performed as per standard local practice. Exact time point for CT scan will depend on the investigator's standard plan at each site (see Section 7.2.7).
- Check and record concomitant medications (not including NSCLC treatment regimen).
- NSCLC treatment regimen and any dose adjustments, as and if applicable.

- New study kit will be dispensed, and patient will return wallet card from previous visit; compliance will be checked.
- The patient will also be reminded about the prohibited concomitant medications (see Section 5.13.2 for details).
- Patient will also be reminded to come back to clinical site in 3 weeks for next visit and be reminded to arrive at the hospital under fasting conditions.

6.1.4 Visit 4 (Day 43+3days): Week 6

The patient will return to the trial site on Visit 4, at Day 43 (+3), approximately 3 weeks after Visit 3. Patient will arrive at the hospital under fasting conditions.

The patient will undergo the following procedures/assessments:

- Study drug administration.
- Laboratory assessments, including:
  - Chemistry,
  - Hematology.
- Vital signs including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Body weight via scale measurement, to be done prior to study drug administration.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); Results of this PE will be inserted in source data and in the relevant pages of eCRF.
- 12-Lead ECG (1 hour post dose), in triplicate.
- CT scan may be performed as per standard local practice. Exact time point for CT scan will depend on the investigator's standard plan at each site (see Section 7.2.7).
- Adverse Events, procedures, and hospitalizations assessment.
- Administration and completion of
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB domains of FACT-G, 12-item A/CS domain and FACIT-F fatigue domain),
  - PGIS and PGIC questionnaires for body weight, anorexia and overall conditions,
  - Hunger Assessment questionnaire.

Questionnaires will be administered in the order presented here and administered from 1 to 4 hours post study drug administration.

- Check and record Concomitant medications (not including NSCLC treatment regimen).
- NSCLC treatment regimen and any dose adjustments, as and if applicable.

- New study kit will be dispensed, and patient will return wallet card from previous visit; compliance will be checked.
- The patient will also be reminded about the prohibited concomitant medications (see Section 5.13.2 for details).
- Patient will also be reminded to come back to clinical site in 3 weeks for next visit and be reminded to arrive at the hospital under fasting conditions.

6.1.5 Visit 5 (Day 64+3 days): Week 9

The patient will return to the trial site on Visit 5, at Day 64 (+3), approximately 3 weeks after Visit 4. Patient will arrive at the hospital under fasting conditions.

The patient will undergo the following procedures/assessments:

- Study drug administration.
- Laboratory assessments, including:
  - Chemistry,
  - Hematology.
- Urine pregnancy test for females of childbearing potential.
- Urinalysis under fasting status.
- Vital signs including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- ECOG PS.
- Body weight via scale measurement, to be done prior to study drug administration.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); results of this PE will be inserted in source data and in the relevant pages of eCRF.
- 12-Lead ECG (1 hour post dose), in triplicate.
- CT scan may be performed as per standard local practice. Exact time point for CT scan will depend on the investigator's standard plan at each site (see Section 7.2.7).
- Adverse Events, procedures, and hospitalizations assessment.
- Administration and completion of
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB domains of FACT-G, 12-item A/CS domain and FACIT-F fatigue domain).
  - PGIS and PGIC questionnaires for body weight, anorexia and overall conditions.
  - Hunger Assessment questionnaire.

Questionnaires will be administered in the order presented here and administered from 1 to 4 hours post study drug administration.

- Check and record Concomitant medications (not including NSCLC treatment regimen).
- NSCLC treatment regimen and any dose adjustments, as and if applicable.
- New study kit will be dispensed, and patient will return wallet card from previous visit; compliance will be checked.
- The patient will also be reminded about the prohibited concomitant medications (see Section 5.13.2 for details).
- Patient will also be reminded to come back to clinical site in 3 weeks for next visit and be reminded to arrive at the hospital under fasting conditions.

6.1.6 Visit 6 (Day 85+3): Week 12

The patient will return to the trial site on Visit 6, at Day 85 (+3), approximately 3 weeks after Visit 5. Patient will arrive at the hospital under fasting conditions.

The patient will undergo the following procedures/assessments:

- Study drug administration.
- Laboratory assessments, including:
  - Chemistry,
  - Hematology,
  - HbA1c Assessment.
- Vital signs including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Body weight via scale measurement, to be done prior to study drug administration.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); Results of this PE will be inserted in source data and in the relevant pages of eCRF.
- 12-Lead ECG (1 hour post dose), in triplicate.
- CT scan may be performed as per standard local practice. Exact time point for CT scan will depend on the investigator's standard plan at each site (see Section 7.2.7).
- Adverse Events, procedures, and hospitalizations assessment.
- Administration and completion of
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB domains of FACT-G, 12-item A/CS domain and FACIT-F fatigue domain),
  - Hunger Assessment questionnaire.

Questionnaires will be administered in the order presented here and administered from 1 to 4 hours post study drug administration.

- Check and record Concomitant medications (not including NSCLC treatment regimen).
- NSCLC treatment regimen and any dose adjustments, as and if applicable.
- CT scan at all sites as per standard local practice.
- New study kit will be dispensed, and patient will return wallet card from previous visit; compliance will be checked.
- The patient will also be reminded about the prohibited concomitant medications (see Section 5.13.2 for details).
- Patient will be reminded to come back to clinical site in 3 weeks for next visit and be reminded to arrive at the hospital under fasting conditions.

6.1.7 Visit 7 (Day 106+3): Week 15

The patient will return to the trial site on Visit 7, at Day 106 (+3), approximately 3 weeks after Visit 6. Patient will arrive at the hospital under fasting conditions.

The patient will undergo the following procedures/assessments:

- Study drug administration.
- Laboratory assessments, including:
  - Chemistry,
  - Hematology.
- Vital signs including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Body weight via scale measurement, to be done prior to study drug administration.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); results of this PE will be inserted in source data and in the relevant pages of eCRF.
- 12-Lead ECG (1 hour post dose), in triplicate.
- CT scan may be performed as per standard local practice. Exact time point for CT scan will depend on the investigator's standard plan at each site (see Section 7.2.7).
- Adverse Events, procedures, and hospitalizations assessment.
- Administration and completion of
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB domains of FACT-G, 12-item A/CS domain and FACIT-F fatigue domain),
  - Hunger Assessment questionnaire,

Questionnaires will be administered in the order presented here and administered from 1 to 4 hours post study drug administration.

- Check and record Concomitant medications (not including NSCLC treatment regimen).
- NSCLC treatment regimen and any dose adjustments, as and if applicable.
- New study kit will be dispensed, and patient will return wallet card from previous visit; compliance will be checked.
- The patient will also be reminded about the prohibited concomitant medications (see Section 5.13.2 for details).
- Patient will also be reminded to come back to clinical site in 3 weeks for next visit and be reminded to arrive at the hospital under fasting conditions.

6.1.8 Visit 8 (Day 127+3) – Week 18

The patient will return to the trial site on Visit 8, at Day 127 (+3), approximately 3 weeks after Visit 7. Patient will arrive at the hospital under fasting conditions.

The patient will undergo the following procedures/assessments:

- Study drug administration.
- Laboratory assessments, including:
  - Chemistry,
  - Hematology.
- Vital signs including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Body weight via scale measurement, to be done prior to study drug administration.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); results of this PE will be inserted in source data and in the relevant pages of eCRF.
- 12-Lead ECG (1 hour post dose), in triplicate.
- CT scan may be performed as per standard local practice. Exact time point for CT scan will depend on the investigator's standard plan at each site (see Section 7.2.7).
- Adverse Events, procedures, and hospitalizations assessment.
- Administration and completion of
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB domains of FACT-G, 12-item A/CS domain and FACIT-F fatigue domain),
  - Hunger Assessment questionnaire.

Questionnaires will be administered in the order presented here and administered from 1 to 4 hours post study drug administration.

- Check and record Concomitant medications (not including NSCLC treatment regimen).
- NSCLC treatment regimen and any dose adjustments, as and if applicable.
- New study kit will be dispensed, and patient will return wallet card from previous visit; compliance will be checked.
- The patient will also be reminded about the prohibited concomitant medications (see Section 5.13.2 for details).
- Patient will also be reminded to come back to clinical site in 3 weeks for next visit and be reminded to arrive at the hospital under fasting conditions.

6.1.9 Visit 9 (Day 148+3): Week 21

The patient will return to the trial site on Visit 9, at Day 148 (+3), approximately 3 weeks after Visit 8. Patient will arrive at the hospital under fasting conditions.

The patient will undergo the following procedures/assessments:

- Study drug administration,
- Laboratory assessments, including:
  - Chemistry,
  - Hematology.
- Vital signs including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Body weight via scale measurement, to be done prior to study drug administration.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); Results of this PE will be inserted in source data and in the relevant pages of eCRF.
- 12-Lead ECG (1 hour post dose), in triplicate.
- CT scan may be performed as per standard local practice. Exact time point for CT scan will depend on the investigator's standard plan at each site (see Section 7.2.7).
- Adverse Events, procedures, and hospitalizations assessment.
- Administration and completion of
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB domains of FACT-G, 12-item A/CS domain and FACIT-F fatigue domain),
  - Hunger Assessment questionnaire.

Questionnaires will be administered in the order presented here and administered from 1 to 4 hours post study drug administration.

- Check and record Concomitant medications (not including NSCLC treatment regimen).

- NSCLC treatment regimen and any dose adjustments, as and if applicable.
- New study kit will be dispensed, and patient will return wallet card from previous visit; compliance will be checked.
- The patient will also be reminded about the prohibited concomitant medications (see Section 5.13.2 for details).
- Patient will also be reminded to come back to clinical site in 3 weeks for next visit and be reminded to arrive at the hospital under fasting conditions.

6.1.10 Visit 10 (Day 169+3): Week 24

The patient will return to the trial site on Visit 10, at Day 169 (+3), approximately 3 weeks after Visit 9. Patient will arrive at the hospital under fasting conditions.

The patient will undergo the following procedures/assessments:

- Patient will return wallet card from previous visit; compliance will be checked.
- Study drug administration (last dose).
- Laboratory assessments, including:
  - Chemistry,
  - Hematology,
  - HbA1c Assessment.
- Urine pregnancy test for females of childbearing potential.
- Urinalysis under fasting status.
- Vital signs including pulse rate, systolic and diastolic blood pressure after at least 5 minutes rest in semi-supine position, respiratory rate and body temperature).
- Body weight via scale measurement, to be done prior to study drug administration.
- A dedicated physical examination with focus to monitoring signs and symptoms of edema (see Section 7.2.2.1 for details); Results of this PE will be inserted in source data and in the relevant pages of eCRF.
- 12-Lead ECG (1 hour post dose), in triplicate.
- CT scan may be performed as per standard local practice. Exact time point for CT scan will depend on the investigator's standard plan at each site (see Section 7.2.7).
- Adverse Events, procedures, and hospitalizations assessment.
- Administration and completion of
  - FACIT questionnaires (includes all 4 domains PWB, FWB, SWB, and EWB domains of FACT-G, 12-item A/CS domain and FACIT-F fatigue domain),
  - Hunger Assessment questionnaire.

Questionnaires will be administered in the order presented here and administered from 1 to 4 hours post study drug administration.

- Check and record Concomitant medications (not including NSCLC treatment regimen).
- NSCLC treatment regimen and any dose adjustments, as and if applicable.
- Patient will also be reminded that will be contacted by study stuff for follow-up visit in two weeks.

6.1.11 Visit 11 (Follow-up visit): Week 26

A follow-up visit, at Day 183 (+3), approximately 2 weeks after Visit 10 will be conducted over the telephone.

The patient will undergo the following procedures/assessments:

- Patient will be inquired for safety; information related to AEs, procedures, and hospitalizations' assessment will be collected over telephone.

6.2 Definition of study Completion

A patient will be defined as having "completed" the study when the patient completes Visit 11. Termination of the study before performing Visit 11 will be considered as a premature study discontinuation.

Overall study end date is defined as the date of last patient's last visit.

6.3 Premature Discontinuation of Study Drug

Patients may withdraw their consent and discontinue the study treatment at any time. Every effort should be made to encourage patients to return for scheduled visits to undergo study procedures even if they discontinue study drug. Patients who prematurely discontinue will be classified as follows (only one category may be selected):

1. An AE occurs that, in the opinion of the Investigator, makes it unsafe for the patient to continue in the study.
2. The patient is lost to follow-up.
3. The patient dies.
4. The patient withdraws consent.
5. The Investigator, for any reason, terminates the entire study, or terminates the study for that patient; or the attending physician requests that the patient be withdrawn for any medical reason.
6. The Sponsor or the Regulatory Authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular patient.

If a patient is discontinued from the study after treatment with the investigational medicinal product, the Investigator must try his/her best to contact the patient for scheduled visits especially Week 9 (64+3) visit assessments in view of completing the study safety assessment by collecting information that may be suggestive of AEs. Every effort will be made to collect data from the protocol-specified assessments; patients will be asked to

continue to participate in the study and complete planned visits up to the end of the treatment period (Week 24) even if they have permanently discontinued treatment with anamorelin/placebo (“retrieved dropout” approach).

Patients discontinued after randomization will not be replaced.

6.4 Diet and Lifestyle

There are no dietary restrictions during the study. Patients will receive standard dietary counseling as per the routine clinical practice.

Subjects will be instructed to refrain from any alcohol use from 48 hours prior to their first treatment and throughout the duration of the study. As per National Institute on Alcohol Abuse and Alcoholism (NIAAA), in the United States, one "standard" drink contains roughly 14 grams of pure alcohol, which is found in: a) 12 ounces (~ 360 ml) of regular beer, which is usually about 5% alcohol; b) 5 ounces (~ 150 ml) of wine, which is typically about 12% alcohol; c) 1.5 ounces (~ 50 ml) of distilled spirits, which is about 40% alcohol.

Excessive alcohol use is according to Substance Abuse and Mental Health Services Administration (SAMHSA) is a binge drinking on 5 or more days in the past month.

Binge drinking is ≥ 5 drinks for males or ≥ 4 drinks for females on the same occasion (i.e., at the same time or within a couple of hours of each other) on at least 1 day in the past month.

There are no restrictions on exercise or activity.

7 METHODS OF ASSESSMENT

7.1 Efficacy Assessments

Primary efficacy assessments include body weight and anorexia symptoms via the 5-item Anorexia Symptom Subscale.

Other assessments include other scoring derived from the FAACT (total domain score and the 4-item Anorexia Concerns Subscale derived from the FAACT), as well as additional patient-reported outcome assessments including the FACIT-F, Hunger Assessment Scale, PGIS and PGIC questionnaires for body weight, anorexia and overall conditions.

All questionnaires will be provided to the sites and will be completed by the patients at the specified visits. Every effort should be made to have the patient complete the questionnaires alone. If they cannot physically complete them by themselves, then site personnel may read the questions to the patients and record their answers. Patient caregivers should not influence/contribute to patient responses.

These instruments will be provided in appropriate validated translations and will be completed by the patients in their native language.

The PRO data will be collected by the mean of electronic diary, the data will be automatically transferred and the sum score of the different questionnaires used for screening and randomization purposes will be displayed on the device.

Site personnel should ensure all questions were answered and that the intended answers were clearly marked. The site personnel should ask the patient to complete any missed questions and to clarify any unclear answers. If a patient is unable to complete the questions, the reason must be documented in the source documentation and in the eCRF. The order of the questionnaires to be completed at each visit is specified within the study flow chart.

7.1.1 Assessment of Body Weight

Data from literature [Patel-2013] and post-hoc analyses of the previous Phase 3 anamorelin studies suggest that increases in body weight of a magnitude of ≥ 5% from baseline are relevant, associated with corresponding improvements in anorexia-related concerns proximal to the weight loss, and are noticeable and clinically meaningful to patients.

Body weight will be measured in kg at each visit (for details see study flow chart). Measurements will be performed by a Sponsor-trained and certified healthcare professional.

Body weight will be assessed for the purpose of primary, secondary and exploratory efficacy endpoints, as indicated in Section 3.

Calibrated and validated scale will be used at every visit, including screening visit (Visit 1). Scales will be used on hard flooring, such as tile, wood, or cement for accuracy of measurement. Sites will be instructed to weigh the participants at approximately the same time of the day every visit, on empty stomach (in the morning, before breakfast). Study participants will be instructed to remove shoes and clothing for accurate weight

measurement. Patients will be weighed wearing only a hospital gown or hospital scrubs and, if desired, underwear only. Sponsor will make sure the same scale is used at each site.

7.1.2 Assessment of anorexia symptoms and other patient reported outcomes

In this study, three different types of patient-reported outcome measures will be administered to patients, following instructions provided in study flow chart. These questionnaires are listed below, and additional details are provided in each of the following sections:

- FACIT measurements,
- PGI System,
- Hunger Assessment Scale.

7.1.3 Patient Reported Outcome

7.1.3.1 FACIT measurements (Functional Assessment of Chronic Illness Therapy)

This is a collection of questionnaires targeted to the management of chronic illness [FACIT.org] and includes (please see APPENDIX 4 for details):

- **FAACT-A/CS** (Functional Assessment Anorexia Cachexia Therapy): this domain is a 12-item measure of patients' perceptions of anorexia/cachexia symptoms and concerns [Ribaudo-2001]. From this questionnaire the 5-item section referring to anorexia symptoms will be used to assess primary efficacy endpoint.
- **FACIT-F** (Fatigue): this domain is a 13-item measure specifically to address the physical and functional consequences of fatigue [FACIT.org].
- **FACT-G** (Functional Assessment Cancer Therapy- General Version); this 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. For this study, patients will be administered all four domains.

Regarding FACIT questionnaires, 5-item Anorexia Symptom Subscale and a 4-item Anorexia Concerns Subscale have been developed by Helsinn from the FAACT A/CS domain, whereby the validity of both are supported through a qualitative study in NSCLC patients and a retrospective psychometric evaluation using data from the two previous Phase 3 trials with anamorelin [Gelhorn-2016].

In terms of scoring the questionnaires, all negatively worded item responses are reverse coded and summed in accordance with the recommendations of the FACIT Administration and Scoring Guidelines so that higher scores indicate lower levels of QoL/symptom burden (see APPENDIX 5 for details).

Definitions of the different scores from these questionnaires, are as follows:

- **FACT-G total score:** obtained by summing Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being subscale scores of the FACT-G; the range of possible scores is 0-108.
- **FAACT total score:** obtained by summing the FACT-G and the A/CS domain; the range of possible scores is 0-156.
- **FAACT TOI:** obtained by summing the Physical Well-Being and Functional Well-Being subscale scores of the FACT-G plus the A/CS domain; the range of possible scores is 0-104.
- **FAACT A/CS Domain:** obtained by summing the 12-items of the A/CS domain; the range of possible scores is 0-48,
- **5-item Anorexia Symptom Subscale:** obtained by summing the 5 anorexia symptom items derived from the A/CS domain (i.e., *"good appetite," "interest in food drops," "food tastes unpleasant," "get full quickly," and "difficulty eating rich/heavy foods*"); the range of possible scores is 0-20
- **4-item Anorexia Concerns Subscale:** obtained by summing the 4 anorexia concern items derived from the A/CS domain (i.e., "*amount I eat sufficient," "worried about weight," "concerned about thinness," and "pressured to eat*"); the range of possible scores is 0-16,
- **FACIT-F Fatigue Domain:** obtained by summing the 13-items of the fatigue domain; the range of possible scores is 0-52,
- **FACIT-F TOI:** obtained by summing the Physical Well-Being and Functional Well-Being subscale scores of the FACT-G plus the fatigue domain; the range of possible scores is 0-108.

7.1.3.2 PGI (Patient Global Impression) System

This is a collection of two questionnaires (please see APPENDIX 6 for details):

- **PGIS (Patient Global Impression of Severity):** This is a two-items PRO, each with a 4-point Likert-type response scale, one ranging from ''do not have" symptoms to "severe" symptoms related to appetite/eating, and the other one ranging from ''have not had" concerns to "have had severe" concerns related to weight.

- **PGIC (Patient Global Impression of Change):** This is a three-item PRO (overall, anorexia and body weight), each with a 7-point Likert-type response scale ranging from ‘‘very much worse’’ to ‘‘very much improved’’ appetite/eating-related symptoms and overall condition.

7.1.3.3 HAS (Hunger Assessment Scale)

This questionnaire consists of two questions and each question can be ranked from 0 (not at all) to 4 (very much) scale (please see APPENDIX 7 for details).

7.2 Safety Assessments

7.2.1 Demographic/Medical History

A complete medical history will be recorded at the Screening Visit and will include evaluations for past or present conditions. Demographic information (including age, gender, race and ethnicity) and information on histological or cytological tumor type, genotype and treatment will also be collected at the Screening Visit.

7.2.2 Physical examination

A complete physical examination will be performed by principal or sub investigator, as applicable at Visit 1 (Screening Visit) and at each visit during the treatment period [Visit 2 (Week 1), Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), Visit 7 (Week 15), Visit 8 (Week 18), Visit 9 (Week 21), and Visit 10 (Week 24)]. This evaluation will include an examination of general appearance, head, eyes, ears, nose, throat, skin, neck, lungs, cardiovascular, breast, lymph nodes, abdomen, musculoskeletal and neurological. For details see study flow charts.

Information about the physical examinations will be recorded in the source documentation at the site and any abnormalities at screening will be recorded in the eCRF. After signing the informed consent, any new or worsening of existing pathological findings noted since previous examination performed under the present protocol should be reported on the Adverse Event eCRF form.

7.2.2.1 Monitoring Signs and symptoms of edema

Since excess in body water may contribute to a change in body weight and confound the primary efficacy analysis, all patients will be monitored for the signs and symptoms of edema during the study. Signs and symptoms of edema will be recorded in patient charts at each study visit. For scheduling details see study flow chart.

A dedicated PE aiming to monitor signs and symptoms of edema should be performed on limbs, abdominal and thoracic landmarks. Edema should be evaluated for pitting, tenderness to palpation (by applying pressure), and skin temperature, color, and texture changes.

Limbs Edema:

PE should focus on dorsum of the foot, all foot including ankle, the medial malleolus, and the bony portion of the tibia. In general, PE should focus on the assessment of edema involving all part of limb distal to middle point (knee, elbow), all limb involved from proximal joint (hip, elbow), and all limbs.

Abdominal and Thoracic Edema

PE should focus on visual and palpation assessment of the abdominal area, while for the evaluation of thoracic edema will be complemented by auscultation.

Data of patients with fluid retention will be handled as described in Section 9.4.1.

7.2.3 Vital signs

Vital signs will be measured at Visit 1 (Screening Visit) and at each visit during the treatment period [Baseline Visit 2 (Week 1), Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), Visit 7 (Week 15), Visit 8 (Week 18), Visit 9 (Week 21), and Visit 10 (Week 24)], for details see study flow charts.

Vital sign assessments include body temperature, pulse rate, blood pressure (systolic and diastolic), and respiratory rate. Pulse rate, systolic and diastolic blood pressure will be measured after the patient has been resting in the semi-supine position for at least 5 minutes.

7.2.4 Height and BMI

Height will be measured in cm at the Screening Visit (Day -7 to -1, Week -1), and BMI will also be calculated and recorded.

7.2.5 12-lead ECG

12-lead ECGs will be conducted in triplicate at each visit Screening Visit, Visit 2 (Week 1), Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), Visit 7 (Week 15), Visit 8 (Week 18), Visit 9 (Week 21), and Visit 10 (Week 24). These 12-lead ECGs will be obtained in triplicate at each time-point and the reading will be carried out at a central facility by an independent cardiologist blind to the study treatment. Any new or worsening ECG abnormalities assessed to be clinically significant by each study investigator will be reported as adverse events.

ECG will be recorded in triplicate at 1 hour (±5 minutes) post dose at each visit to align with occurrence of C_{max}, with the exception of Screening Visit (where ECG will be taken only pre-dose) and Visit 2, Day 1, where ECG will be taken also at pre-dose.

7.2.6 Clinical Laboratory Tests

Samples for safety laboratory assessments will be taken in fasting conditions at pre-set time points as specified in the study flow charts. All samples will be sent to the central laboratory for analysis. The instructions on how the samples must be processed and shipped will be provided to the Investigator in the relevant laboratory manual.

HbA_{1c} will be performed at Visit 1 (Screening visit), Visit 6 (Week 12), and Visit 10 (Week 24) visits.

7.2.6.1 Hematology

The hematology assessments will include CBC with differential count and will be performed at every visit: Screening Visit, Visit 2 (Week 1), Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), Visit 7 (Week 15), Visit 8 (Week 18), Visit 9 (Week 21), and Visit 10 (Week 24).

7.2.6.2 Blood Chemistry

Blood Chemistry will include sodium, potassium, chloride, calcium, total protein, albumin and pre-albumin, AST (SGOT), alkaline phosphatase (ALP), ALT (SGPT), total bilirubin, creatinine, C-reactive protein and glucose. These will be performed at every visit in fasting state: Screening Visit, Visit 2 (Week 1), Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), Visit 7 (Week 15), Visit 8 (Week 18), Visit 9 (Week 21), and Visit 10 (Week 24).

7.2.6.3 Urinalysis

Urinalysis will be performed at Visit 1 (Screening), Visit 5 (Week 9), and Visit 10 (Week 24). Urinalysis will be performed pre-dose and under fasting conditions and will include protein, glucose, WBC, erythrocytes, and bacteria.

7.2.6.4 Pregnancy Screen

Urine pregnancy testing for women of childbearing potential only will be performed at Screening visit (Week -1), Visit 2 (Week 1), Visit 5 (Week 9), and Visit 10 (Week 24).

7.2.7 CT scan for Tumor Assessment

All patients will undergo CT scan assessment as per standard local practice for tumor assessment. Responses will be evaluated by the Investigator according to RECIST 1.1 and will be recorded on the eCRF.

It is upon the judgment of the investigator, following local practice for CT scan frequency and according to patient overall clinical conditions, to decide applicability and timing of CT scan during the course of the study, including screening visit.

For CT scans performed earlier than 28 days prior to first dose of anamorelin, and for data traceability purpose, it is kindly requested to report date on the eCRF, as available even if date is earlier than 28 days prior to first dose of anamorelin.

Tumor responses, including disease progression, will be evaluated by the Investigator according to RECIST 1.1 [Eisenhauer-2009] and will be recorded in the eCRF.

8 ADVERSE EVENTS

AE recording will begin at the time the informed consent form is signed. Thereafter, AEs will be ascertained by asking the patient how he/she has been since the last visit.

8.1 Definition of Adverse Events

Adverse Event (AE)

As defined by the current ICH Guideline for Good Clinical Practice [ICH-2002] an Adverse Event (AE) is:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Within the scope of this study, such untoward medical occurrences would be considered as "AEs" even if the subject was not administered the study drugs but had already signed the Informed Consent Form.

AEs include the following types of occurrences:

- Suspected adverse drug reactions
- Other medical experiences, regardless of their relationship to the study drugs, such as injury, surgery, accidents, increased severity of pre-existing symptoms, apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, physiological testing, or physical examination findings
- Reactions from drug overdose, abuse, withdrawal, hypersensitivity, or toxicity.

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

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.

Unexpected Adverse Event

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

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 based on patient's clinical evaluation.

8.1.1 Classification of Adverse Events

The Investigator will classify AEs based on their severity and relationship to IMP. Every effort must be made by the Investigator to categorize each AE according to its severity (see Section 8.1.1.1 Severity), and its relationship (see Section 8.1.1.2 Relationship to Investigational Medicinal Product).

8.1.1.1 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) (for details please refer to the integral document Terminology Criteria for Adverse Events [CTCAE-2017]; USA Department of Health and Human Services, National Institutes of Health, National Cancer Institute), 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.

8.1.1.2 Relationship to Investigational Medicinal Product

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

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 aetiologies, 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 aetiologies 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 aetiologies. 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 aetiologies.
Unlikely related	It is more likely that the event is due to other aetiologies 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 aetiology 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.
Unassessable	The data are insufficient or contradictory to make a meaningful medical assessment.

8.1.2 Reporting Adverse Events

AE reporting has to be in accordance with the ICH E6 Guidance on GCP and ICH E2A Guidance on Clinical Safety Management [ICH-1997; ICH-1994].

During the course of the study, all AEs (including SAEs), irrespective of the relatedness to the study drugs, must be recorded in detail in the source records and transcribed onto the AEs pages of the eCRF. During each monitoring visit, the Investigator and the site monitor will review all AEs and perform Source Data Verification (SDV). The Investigator will be responsible for ensuring that the correct information concerning all AEs is entered on the appropriate eCRF pages.

In case clinically significant laboratory abnormalities are detected, the etiology of the abnormality should be identified, and the diagnosis should be recorded as an AE. Otherwise, if the etiology cannot be identified, the laboratory abnormality as such should be recorded as the AE.

Similarly, clinically significant laboratory abnormalities detected at the screening visit (before any administration of the investigational medicinal product or additional non-investigational drug), if not justified by an underlying disease already recorded in the medical history, are to be recorded as AEs.

The reporting period for AEs is the period starting from the time of Informed Consent signature and lasting until Day 183 (+3) days post study drug administration on Day 1. All unresolved AEs (including SAEs) will be documented on the eCRF as “ongoing”.

8.1.2.1 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest are defined as pre-specified events, under monitoring by the Sponsor and for which detailed information by the Investigator may be needed.

In this study protocol AESIs are considered the following:

1. AST increase (CTCAE G ≥ 3)
2. ALT increase (CTCAE G ≥ 3)
3. Presyncope
4. Syncope
5. Ventricular arrhythmia (CTCAE G ≥ 3)
6. Heart failure (CTCAE G ≥ 3)
7. Unexplained sudden death
8. Seizure (any CTCAE Grade)
9. Hyperglycemia (CTCAE G ≥ 3)

8.1.2.2 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. An overdose is the accidental or intentional use

of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All overdoses should be recorded, independently from an association with AEs.

All AEs associated with an overdose or incorrect administration of study drug should be recorded. If an overdose results in an SAE, it must be reported to the Sponsor as an SAE within 24 hours of identifying the event.

8.1.3 Reporting Serious Adverse Events

All SAEs occurring from the time of signing of the informed consent until Follow-up period must be reported immediately to the safety desk of the CRO. Information on the contact details are provided in the Investigator file as well as at Section General Information of the present protocol. The Investigator or designated study coordinator must report the SAE to the CRO within 24 hours of observation or notification of a serious AE. All of these events must also be recorded on the appropriate eCRF pages.

It is the responsibility of the Investigator to inform his or her local Institutional Review Board (IRB)/Ethics Committee (EC) about SAEs according to the local IRB/EC requirements. It is the responsibility of the Sponsor (or Sponsor's designee) to submit applicable SAE Reports to the Competent Authorities. Reporting of suspected unexpected serious adverse reactions (SUSARs) to the relevant IRB/EC, in accordance with the EU Clinical Trial Directive 2001/20/EC, the US Code of Federal Regulations 313.32 and ICH E6 Guidance on GCP and ICH E2A Guidance on Clinical Safety Management, will also be the responsibility of the Sponsor (or Sponsor's designee) [ICH-1997; ICH-1994].

A safety contact sheet will be provided to the Investigator and will be maintained in the Investigator file at the site. Instructions will be provided to the investigators for submission of the SAEs to the CRO.

Any serious and unexpected AE that the Investigator or the Sponsor considers to be at least possibly related to study drug is subject to expedited reporting to the appropriate Health Authorities. Events for which causality is unknown/unassessable or unreported by the Investigator are considered to be possibly related.

The procedure to unblind a patient is described in Section 5.9.

8.1.3.1 Follow-up of Serious Adverse Events

SAEs will be followed by the Investigator until the outcome is resolved, has reached a stable condition in the Investigator's opinion, or until the patient is lost to follow-up. When the investigational site receives any information about a serious adverse event which changes or adds further information about the initial SAE, the site will send this information within 24 hours to the safety desk of the CRO, especially if this new information has an effect on the seriousness, relatedness or expectedness of an adverse event.

8.1.4 Pregnancy Report

In the unlikely eventuality that a patient becomes pregnant during the trial, the Investigator will be requested to complete the Pregnancy Report Form and any relevant document. They must be forwarded to the CRO e-mail address or sent by mail or fax (see Section General Information). After check of consistency, designated personnel at the CRO will then forward the information to the Sponsor within 24 hours of becoming aware of the pregnancy. Even though pregnancy is not considered as SAE itself, pregnancy has to be reported within the timelines as defined for SAE.

Pregnant patients will be followed by the Investigator and CRO / Sponsor until the fetus / newborn is delivered. At the study end and database closure, reports of Pregnancy Outcome will be sent by the sites directly to Helsinn Safety. The subject's primary care physician (or obstetrician) will be requested by the Investigator to provide further information on the pregnancy using the Pregnancy Outcome Information Form. If pregnancy occurs while the patient is on study treatment or up to 28 days after last study drug administration, the subject will be discontinued from the study.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study and gives consent to collect information, the investigator must fill the pregnancy form and forward it to the CRO. The pregnancy must be followed for the final pregnancy outcome and the development of the child after birth. The pregnancy outcome form must be filled in by the investigator and sent to the study sponsor.

9 STATISTICS

This section summarizes the statistical principles and methods planned to analyze the data for the ANAM-17-20 clinical study. The reference document is the ICH Topic E9(R1) Statistical Principles for Clinical Trials: Note for Guidance on Statistical Principles in Clinical Trials [ICH-1998].

Further details of the statistical analyses and data presentations to be used in reporting the study will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to breaking the blind. Changes from analyses planned in this protocol will be documented in the SAP and/or study report. The database will be locked after all queries are resolved, and a blinded review of data is performed, and decisions made about study populations and handling of unused or missing data.

9.1 Stratification factors

The stratification aims to balance investigational treatment within group of prognostic factors.

Central randomization will be stratified by line of systemic anti-cancer treatment (first line vs second line vs third line), by type of anti-cancer therapy (immunotherapy vs non-immunotherapy) and by Baseline score of 5-item Anorexia Symptom Subscale (≤10 vs >10).

9.2 Sample Size Determination

At the time the trial was initiated, the primary endpoint was the Composite Clinical Response (CCR) rate. The sample size was determined based on results obtained on patients participating to the previous trials (HT-ANAM-301 and HT-ANAM-302). A logistic regression of the CCR on the randomized treatment with a sample size of 316 patients (158 patients per arm) would achieve 90% power at a 2-sided 0.05 significance level to detect a change in CCR from the placebo expected rate of 0.075 to 0.200. This level of effect corresponds to an odds ratio of 3.083. (SAS® - PROC POWER)

From the v4.A, the protocol has been amended in order to change from a primary efficacy endpoint based on the CCR at week 9 to two co-primary efficacy endpoints: the duration of treatment benefit in weight at Week 12, and duration of treatment benefit in 5-item Anorexia Symptom Subscale at Week 12.

Adequate power was confirmed by simulation for those co-primary endpoints (joint power greater than 90%). However, during the course of the study an error was discovered in the algorithm used to determine the statistical power for the evaluation of the duration of treatment benefit from baseline to Week 12 for body weight and anorexia (5-IASS) co-primary endpoints. New simulations correcting for the programming error were performed and these results confirmed high power (over 98%) for the weight-based co-primary endpoint but showed low power for the 5-IASS co-primary endpoint (between 60 and 70%).

Power for the new co-primary endpoints (mean change in body weight and mean change in 5-IASS) with the fixed sample size of 158 patients per arm was computed by means of

simulations. Power for mean change in body weight was showed to be close to 100%, while power for mean change in 5-IASS was showed to range between 78% and 87%, so leading to a joint power for the two co-primary endpoints of at least 78%.

9.3 Definition of Study Populations for Analysis (Analysis Set)

Study populations are defined as follows:

Safety Set

The Safety Set includes all patients who receive any study drug and will be analyzed as per actual treatment.

ITT Set

The Intent-to-Treat (ITT) Set includes all randomized patients and will be analyzed as per planned treatment.

Full Analysis Set

The Full Analysis Set (FAS) includes all randomized patients who take at least one dose of trial medication, and for which post randomization data are collected. The definition may be updated at the time of the blind review of the data at the end of the trial.

Per-Protocol (PP) Set

The Per-Protocol Set is the subset of the randomized patients who do not have major protocol violations.

9.4 Statistical Analysis

9.4.1 Missing Data

A detailed presentation of missing data will be produced, indicating their amount and incidence by treatment, visit and reason (For instance: visit not done, assessment not done).

Every effort will be made to collect data from the protocol-specified assessments; patients will be asked to continue to participate in the study and complete planned visits up to the end of the treatment period (Week 24) even if they have permanently discontinued treatment with anamorelin/placebo (“retrieved drop-out” approach). Reason for treatment discontinuation will be precisely collected in the CRF and will be used to investigate possible unexpected patterns of missing data and for the imputation itself.

However, due to the nature of the patients’ underlying disease, a non-ignorable amount of missing data is expected in this trial. To minimize the risk of bias in the analysis, ad hoc rules for single/multiple imputation will be adopted. The multiple imputation (MI) method for missing data, is described in the literature [Ratitch -2014; Ratitch -2013].

The missing data of the variables being part of the primary efficacy endpoints (weight, 5-item Anorexia Symptom Subscale score) and the secondary/exploratory efficacy endpoints will be imputed. No imputation will be performed for survival status and no data will be imputed after patient death. All observed data will be included in the analyses, except for

a sensitivity analysis in which the weight of the patients with fluid retention at the date of the assessment will be replaced with imputation approach as if they were missing.

Death from underlying disease is rather inevitable in this target population and does not reflect a failure of study treatment. According to the ICH E9(R1) guideline [ICH-1998], death is considered as an intercurrent event, after which no value is measurable. In order to measure the treatment effect for these patients, the "while alive" strategy will be used. Therefore, only values collected before death for patients dying before the endpoint will be used for the analyses.

9.4.2 Multiplicity

The primary and the secondary efficacy endpoints will be tested using a hierarchy for testing in order to control type I error rate.
The order of testing will be as follows: the co-primary efficacy endpoints related to the mean change in weight (H_{0w}) and related to the mean change in 5-item Anorexia Symptom Subscale (H_{0a}), then the secondary efficacy endpoints: the duration of benefit in weight (≥0) (H_{0d0w}), the duration of benefit in weight (≥ to a predefined threshold) (H_{0dtw}), the duration of benefit in 5-IASS (≥ 0) (H_{0d0a}), the duration of benefit in 5-IASS (≥ to a predefined threshold) (H_{0dta}), then the mean change in FAACT 12-item A/CS domain score (H_{0mF}), in FACIT-F (H_{0mFF}) and in FAACT total score (H_{0mFT}) . Each of these tests will be done sequentially at the level of 0.05 bilateral. The experimental false positive error rate will be preserved because, in order to declare the test component (anamorelin) superior to the placebo, both co-primary endpoints must be significant, meaning that both H_{0w} and H_{0a} must be rejected simultaneously. Additional details are presented in Section 9.4.5.

9.4.3 Subgroups

Subgroup analysis will be conducted for the following subgroups, as far as adequate number of patients in subgroups is confirmed at the BDRM:

- Age (≤ 65 years or > 65 years)
- Gender
- Geographic region
- Systemic anti-cancer treatment line (first line vs second line vs third line) – stratification factor
- Cancer treatment (immunotherapy vs no immunotherapy) – stratification factor
- The 5-item Anorexia Symptom Subscale (≤10 vs >10) – stratification factor
- Patients who completed 24 weeks treatment
- Patients with at least one treatment emergent adverse event with preferred term belonging to fluid retention related (codified under PT 'Fluid retention', 'Ascites', 'Pleural effusion', 'Oedema peripheral', 'Oedema', a specific review of the LLT will be done during the BDRM to confirm if adverse events are possibly impacting the weight measurement) and/or patients with signs of edema as defined in Section 7.2.2.1.
- Race and Ethnicity

9.4.4 Analysis of Demographics, Baseline Variables and Disease Characteristics

Continuous demographic, and baseline characteristics will be summarized using mean, median, SD, Q1, Q3, minimum and maximum, by treatment group and overall.

Qualitative demographic, and baseline characteristics will be summarized by counts and percentages by treatment group.

Demographics and baseline characteristics will be summarized for the ITT, the Safety, the FAS and the Per Protocol analysis sets.

Medical history will be coded with MedDRA dictionary.

Individual subject listing for all data will be provided.

9.4.5 Efficacy Analysis

The efficacy analysis will be performed on the ITT population. Some supportive analyses of the primary efficacy endpoints will be performed on different populations (PP set and FAS set).

The analyses will be produced after the imputation of the missing data. The imputed datasets used for the primary endpoint analysis will be used for the analyses of the secondary and exploratory endpoints. When the data will be considered as missing (see Section 9.4.1), the imputation of the values will be done at the level of the visit for the raw

values (for instance weight). Then, the primary endpoints (for instance mean change in weight) and the secondary endpoints will be derived from the imputed raw values and not directly imputed.

Individual subject listing for all data observed (not imputed) will be provided.

9.4.5.1 Primary Efficacy Analysis

The primary efficacy endpoints are defined in Section 3.1.1

- Mean change in body weight from baseline over 12 Weeks.
- Mean change in 5-item Anorexia Symptom Subscale form baseline over 12 Weeks.

The null hypothesis concerning the first co-primary endpoint of mean change in body weight (H_{0w}) and the corresponding alternative hypothesis (H_{1w}) are defined as:

$$H_{0w}: MW_a = MW_p$$

$$H_{1w}: MW_a \neq MW_p$$

Where MW_a is the mean change in body weight for the anamorelin arm and MW_p is the mean change in body weight for the placebo arm.

The null hypothesis concerning the second co-primary endpoint of mean change in patient 5-item Anorexia Symptom Subscale (H_{0a}) and the corresponding alternative (H_{1A}) are defined as:

$$H_{0a}: MA_a = MA_p$$

$$H_{1a}: MA_a \neq MA_p$$

Where MA_a is the mean change in 5-item Anorexia Symptom Subscale score for the anamorelin arm and MA_p is the mean change in 5-item Anorexia Symptom Subscale score for the placebo arm.

The mean change effect will be computed as mean of the changes from baseline over 12 weeks by the time of the last assessment (either Week 12 or before), and then divided by the number of assessments (observed or imputed) from baseline up to the time of the last assessment (either Week 12 or before, in case of death, for the analysis at Week 12).

The primary efficacy analyses will be conducted on the ITT. H_{0w} and H_{0a} will be tested using an ANOVA to compare the two treatment groups, at a type-I error threshold of 0.05 two-sided. For each of the imputation the estimate of difference between treatments and its standard error (SE) will be computed, then pooled using the Rubin rule, the pooled difference and the related p-value will be interpreted for the primary efficacy analyses. In addition, the least squares (LS)-mean and 95% confidence interval will be presented per treatment group.

9.4.5.2 Sensitivity and supportive analyses of the primary efficacy endpoints

9.4.5.2.1 Sensitivity analyses of the primary efficacy endpoints

The sensitivity analyses are aimed to confirm robustness of the conclusion of the primary efficacy analysis but are not part of the multiplicity adjustment.

A sensitivity analysis regarding imputation of missing will be performed using data from the placebo group only (control-based imputation) for patients who do not have properly matched patients with complete follow-up.

An analysis similar to the primary efficacy analysis will be also conducted after having imputed the values of weight obtained in presence of fluid retention (See Section 9.4.3). The details of the patients regarding the fluid retention will be summarized.

9.4.5.2.2 Supportive analyses of the primary efficacy endpoints

Two analyses similar to the primary efficacy analysis will be conducted, one on the FAS population and another one on the PP for each of the primary endpoints. The FAS and the PP are impacted by the treatment adherence. The results of these analyses are expected to be similar to the one of the primary efficacy analysis.

Primary efficacy endpoints will be presented for all the subgroups (listed in Section 9.4.3).

9.4.5.3 Secondary Efficacy Analysis

All the analyses of the secondary endpoints will be conducted on the ITT.

The secondary endpoints (See Section 3.1.2) will be evaluated following a hierarchal approach, as follows: duration of treatment benefit (≥0) in body weight up to Week 12 as the first secondary endpoint, then duration of treatment benefit (≥ to a predefined threshold) in body weight up to Week 12, duration of treatment benefit (≥0) in 5-IASS up to Week 12, duration of treatment benefit in 5-IASS (≥ to a predefined threshold) up to Week 12, mean change in FAACT 12-item A/CS domain score from baseline up to Week 12, mean change in FAACT total score from baseline up to Week 12 and mean change in FACIT-F from baseline up to Week 12.

The null hypothesis concerning the first secondary endpoint of duration of treatment benefit in body weight (≥0) ((H_{0d0w}) and the corresponding alternative hypothesis (H_{1d0w}) are defined as:

H_{0d0w}: $D_0Wa = D_0W_p$

H_{1d0w}: $D_0W_a \neq D_0W_p$

Where D_0W_a is the duration of treatment benefit in body weight (≥0) for the anamorelin arm and D_0W_p is the duration of treatment benefit in body weight for the placebo arm.

H_{0d0W} will be tested using a two-sided type-I error threshold of 0.05 only if both H_{0w} and H_{0a} (i.e., the null hypothesis concerning the primary endpoints) are rejected.

The null hypothesis concerning the secondary endpoint of duration of treatment benefit in body weight (≥ to a predefined threshold) (H_{0dtW}) and the corresponding alternative (H_{1dtW}) are defined as:

H_{0dtW}: $D_tW_a = D_tW_p$

H_{1dtW}: $D_tW_a \neq D_tW_p$

Where D_tW_a is the duration of treatment benefit in weight (≥ to a predefined threshold) for the anamorelin arm and D_tW_p is the duration of treatment benefit in weight for the placebo arm.

H_{0dtW} will be tested using a type-1 error threshold of 0.05 two sided only if H_{0d0W} (i.e., the null hypothesis concerning the first secondary endpoint) is rejected; note the latter rejection requiring the rejection of if both H_{0w} and H_{0a}.

The following hypothesis systems will then be tested based on the rules above described.

H_{0d0A}: $D_0Aa = D_0A_p$

H_{1d0A}: $D_0A_a \neq D_0A_p$

Where D_0A_a is the duration of treatment benefit in 5-item Anorexia Symptom Subscale (≥0) for the anamorelin arm and D_0A_p is the duration of benefit in 5-item Anorexia Symptom Subscale for the placebo arm.

H_{0dtA}: $D_tAa = D_tA_p$

H_{1dtA}: $D_tA_a \neq D_tA_p$

Where D_tA_a is the duration of treatment benefit in 5-item Anorexia Symptom Subscale (≥ to a predefined threshold) for the anamorelin arm and D_tA_p is the duration of benefit in 5-item Anorexia Symptom Subscale for the placebo arm.

H_{0mf}: $MF_a = MF_p$

H_{1mf}: $MFT_a \neq MF_p$

Where MF_a is the mean change in FAACT 12-item A/CS domain score in the anamorelin arm and MFT_p is the mean change in FAACT 12-item A/CS domain score in the placebo arm. Similar hypothesis systems are set-up for FAACT total score ($H_{0mFt,}$ H_{1mFt}) and FACIT-F ($H_{0mFF,}$ H_{1mFF}).

If the co-primary analysis leads to rejection of H_{0w} and H_{0a}, then the following hypothesis will be tested sequentially: secondary efficacy endpoint related to the duration of treatment benefit in weight (≥0) (H_{0d0w}), the secondary efficacy endpoint related to the duration of treatment benefit in weight (≥ to a predefined threshold) (H_{0dtw}), the secondary efficacy endpoint related to the duration of treatment benefit in 5-IASS (≥0) (H_{0d0A}), the secondary efficacy endpoint related to the duration of treatment benefit in 5-IASS ((≥ to a predefined threshold) (H_{0dtA}) and then the secondary efficacy endpoint related to the mean change in FAACT 12-item A/CS domain score (H_{0mF}), FACIT-F and FAACT total score. Each of these tests will be done sequentially at the level of 0.05 bilateral.

This hierarchy of testing will allow formal confirmation for the effect on the primary endpoints as well as on the secondary endpoints. This will guarantee the study-wise type-1 error, while not requiring any adjustment for multiple testing.

The duration of treatment benefit is measured as the duration for which the patient observed a change from baseline superior or equal to zero or to the predefined thresholds of clinical meaningfulness. For the purpose of computation, it will be assumed a linear evolution between two measurements.

The mean change effect will be computed as mean of the changes from baseline over 12 weeks by the time of the last assessment (either week 12 or before and then divided by the number of assessments (observed or imputed) from baseline up to the time of the last assessment (either week 12 or before, in case of death).

All the secondary endpoints (duration of treatment benefit and mean change from baseline) will be analyzed by means of ANOVA with explanatory variables being the randomized treatment, and the stratification factors.

The least squares (LS)-mean and 95% confidence interval will be presented per treatment group together with the LS-mean treatment effect and its 95% confidence interval. Statistics will be evaluated in each imputed datasets and pooled using Rubin's method.

9.4.5.4 Exploratory Efficacy Analysis

All the analyses of the exploratory endpoints will be conducted on the ITT.

The exploratory efficacy analyses are aimed to explore the effect of the anamorelin on different endpoints but are not part of the multiplicity adjustment, thus have no confirmatory value. The exploratory efficacy endpoints are detailed in Section 3.1.3.

The duration of benefit and mean change from baseline endpoints will be analyzed like the main analysis for the primary efficacy endpoints or the analyses of the secondary endpoints.

All the changes from baseline exploratory endpoints except the HAS and the PGIS/C will be analyzed using an ANCOVA model, with explanatory variables being the randomized treatment, the stratification factors and the baseline value. Specifically, for the imputation of the 5-item Anorexia Symptom Subscale, the stratification based on the 5-IASS baseline will not be introduced in the model as the 5-IASS baseline value itself will be part of the model.

The estimator of the effect will be the difference in change from baseline between the test group and the placebo group estimated as the difference in LS means of the ANCOVA model. The least squares (LS)-mean and 95% confidence interval will be presented per treatment group together with the LS-mean placebo-corrected treatment effect and its 95% confidence interval. Statistics will be evaluated in each imputed datasets and pooled using Rubin's method.

All the responder analyses (CCR and achievement of responder threshold) will be analyzed using a logistic regression, with explanatory variables being the randomized treatment, and the stratification factors. CCR is a composite measure including both a ≥ 5% body weight

gain from baseline and increase ≥ 2 points in the 5-item Anorexia Symptom Subscale score from baseline in patients who survive until the Visits of the analysis. CCR at week 9 was defined as primary efficacy endpoint in protocol version 3.0 and previous editions.

Frequency and rate of responders will be reported with 95% confidence intervals (CIs). For the treatment comparison, the odds ratio will be reported with 95% CIs. Statistics will be evaluated in each imputed datasets and pooled using Rubin's method.

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. In addition, a scatter plot of the change from baseline of the two variables will be presented, with a display of the distribution of each single variable. The analysis will be using all available data at each Study Visit. If a sufficient amount of data will be available, relation between numerical endpoints and survival will be explored, as well as relation between changes in weight and anorexia score at other time points.

9.4.6 Safety Analysis

The safety analysis will be performed on the Safety population.

Clinical evaluations for safety assessments will include adverse events (AEs) assessment, physical examination (PE), vital signs, 12-lead electrocardiogram (ECG), laboratory test (hematology, blood chemistry, urinalysis), Tumor assessments, Overall Survival.

Adverse events, 12-lead ECGs, vital signs, and laboratory assessments will be summarized by treatment group. All safety summaries and analyses will be performed based on the Safety Set. All safety and tolerability data will be listed. A treatment-emergent AE is one with an onset date on or after the date of the first dose of the study drug and up to Visit 11 (Day 183 +3 days) the last study visit.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary (the version will be provided in the SAP and in the Data Management Plan [DMP]) to give a preferred term (PT) and a system organ class (SOC) for each event. The number and percentage of patients who experienced at least one TEAE, drug-related TEAE (defined as AEs with relationship classified by the investigator as definitely, probably, possibly, unassessable or missing), serious TEAE, serious related, severe TEAE (i.e. TEAE with CTCAE grade ≥ 3), AESI (as described below), and the number and percentage of patients withdrawn due to TEAE will be summarized by treatment arm.

For each SOC and PT, summaries will be made with respect to the proportion of patients having at least one occurrence of that event during the study and the total number of events. The incidence of TEAEs in each treatment arm will be presented overall, by SOC and PT, and by additional grouping by severity according to the CTCAE grade and relationship to the study treatment. Tables of TEAEs will be presented by relationship to study drug. Additional tables including any relationship to study drug will be presented.

Adverse events of Special Interest are described in Section 8.1.2.1.

No formal test will be used for "between groups" comparison. All AEs will be listed.

Physical examination results at screening will be summarized in a frequency table (normal/abnormal). Results and relevant findings will be listed.

Vital signs will be summarized by treatment using descriptive statistics for absolute values and change from baseline (i.e., last value before first study drug intake).

Shift tables from baseline to the worst post-baseline results will be provided for the ECG overall interpretation. ECG measurements (HR, QT, QTcF, PR, RR, and QRS) will be summarized by treatment group and visit. Outliers' analysis will be conducted.

Shift tables from baseline to the Last Value according to NCI CTCAE grade will be provided for selected chemistry parameters (ALT, AST, total bilirubin, ALP, creatinine, and glucose) and hematology parameters (hemoglobin, platelet count, white blood cells, neutrophils, and ANC). In addition, a change and % change from baseline will also be measured for HbA1c and pre-albumin.

The best overall tumor responses will be summarized by treatment group with frequencies and percentages.

Overall survival will be described using Kaplan-Meier estimates.

Individual subject listing for all data will be provided.

9.4.7 Determination of the responder threshold in the 5-item Anorexia Symptom Subscale

In order to measure the duration of treatment benefit, the threshold for the changes in 5-IASS will be determined before the unblinding.

Previously, a 2-point threshold to detect clinically meaningful change was determined from a psychometric evaluation using the completed Phase 3 studies (HT-ANAM-301 and HT-ANAM-302) [Gelhorn-2016].

The PGIS and PGIC questionnaires will be administered in this study. Both the PGIS and PGIC will consist of a single question each to assess the severity and change in appetite/eating-related symptoms (for actual questionnaires, see APPENDIX 6). The PGIS is a single-item questionnaire and has a 4-point Likert-type response scale ranging from ''*do not have*" symptoms to "*severe*" symptoms related to appetite/eating. The PGIC is also a single-item questionnaire with a 7-point Likert-type response scale ranging from ''*very much worse''* to ''*very much improved*.'' To note, the terminology of "appetite/eating symptoms" is consistent with that used in the cognitive interviews from a qualitative study (Study EVA-16879-00), as it was seen as more easily interpretable by patients than "anorexia symptoms." The PGIS will be administered at baseline, Week 6 and Week 9, and the PGIC will be administered at Week 6 and Week 9.

The responder definition threshold will be determined as per standard practice for these anchors and supported by distribution-based methods [Norman-2003; Revicki-2008]. Specifically, the responder definition threshold will be determined as the smallest difference or change in score from baseline that is considered important to the patient (i.e., those improving on the PGIS and on the PGIC). As such, the difference in scores on the PGIS from baseline to Week 6 and Week 9 will be determined, and an improvement on the

PGIS will be used to define meaningful change based on mean values of the 5-item Anorexia Symptom Subscale. Similarly, mean values of the 5-item Anorexia Symptom Scale among patients who indicate that their appetite/eating symptoms have improved since starting treatment (based on the PGIC) will be calculated; this value will be used to aid in defining a meaningful change in the symptom measure. The results of these anchor-based methods will be supported by distribution-based methods calculating a 0.2 standard deviation (SD), 0.3 SD, and 0.5 SD, whereby the 0.5 SD estimate can be considered to provide an upper boundary for what would constitute a meaningful change, while 0.2 SD provides a lower boundary [Revicki-2008]. Both anchor-based and distribution-based estimates will be plotted together for comparison and triangulation, whereby different responder thresholds will be graphed to visually depict the range of estimates, and the anchor-based estimates will be assigned more weight than the supportive distribution-based methods. A cumulative distribution of response curve for the 5-item Anorexia Symptom Subscale, one for the treatment group and one for the placebo group, will also be generated to allow a variety of response thresholds to be examined simultaneously and collectively, encompassing all available data.

9.4.8 Determination of the clinically meaningful responder threshold in weight change

In order to measure the duration of treatment benefit, the threshold for the changes in body weight will be determined before the unblinding.

As detailed in Section 1.5, the primary efficacy endpoints has changed during the course of the study due to interaction with FDA. In protocol version 4.0, the patients will be assessed for specific PGIS and PGIC questions related to body weight. The aim of this analysis is to determine which value of percent change from baseline will be suitable to determine a meaningful change.

Briefly, both the PGIS and PGIC will consist of a single question each to assess the level of concern about weight and change in worry about weight (for actual questionnaires, see APPENDIX 6). The PGIS is a single-item questionnaire and has a 4-point Likert-type response scale ranging from ‘‘I have not had any concerns about my weight” to “I have had severe concerns about my weight”. The PGIC is also a single-item questionnaire with a 7-point Likert-type response scale ranging from ‘‘*very much worse’’* to ‘‘*very much improved*.’’ To note, the terminology of “worry about weight” and “weight concerns” is consistent with that used in the cognitive interviews from a qualitative study (Study EVA-16879-00). The PGIS will be administered at baseline, Week 6 and Week 9, and the PGIC will be administered at Week 6 and Week 9.

The responder definition threshold will be determined as per standard practice for these anchors and supported by distribution-based methods [Norman-2003; Revicki-2008]. Specifically, the responder definition threshold will be determined as the smallest difference or change in score from baseline that is considered important to the patient (i.e., those improving on the PGIS and on the PGIC). As such, the difference in scores on the PGIS from baseline to Week 6 and Week 9 will be determined, and an improvement on the PGIS will be used to define meaningful change based on mean values of weight change in

percentage. Similarly, mean values of weight change in percentage among patients who indicate that their weight concerns have improved since starting treatment (based on the PGIC) will be calculated; this value will be used to aid in defining a meaningful change in the concerns measure. The results of these anchor-based methods will be supported by distribution-based methods calculating a 0.2 standard deviation (SD), 0.3 SD, and 0.5 SD, whereby the 0.5 SD estimate can be considered to provide an upper boundary for what would constitute a meaningful change, while 0.2 SD provides a lower boundary [Revicki-2008]. Both anchor-based and distribution-based estimates will be plotted together for comparison and triangulation, whereby different responder thresholds will be graphed to visually depict the range of estimates, and the anchor-based estimates will be assigned more weight than the supportive distribution-based methods. A cumulative distribution of response curve for the weight change in percentage, one for the treatment group and one for the placebo group, will also be generated to allow a variety of response thresholds to be examined simultaneously and collectively, encompassing all available data.

9.5 Interim Analysis

No interim efficacy analysis is planned for this study.

The unblinding of the study will take place only after thresholds for the changes in body weight and 5-IASS have been determined.

10 ETHICAL AND REGULATORY ASPECTS

10.1 Ethical Considerations

The study will be performed in accordance with the principles outlined in the Declaration of Helsinki [Helsinki2013] 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.

10.1.1 Laws and Regulations

This clinical study will be conducted in compliance with all international laws and regulations and national laws and regulations of the countries in which the trial is performed, as well as any applicable guidelines.

10.1.2 Patient's information sheet and informed consent form

All patients 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 native language 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. Patients 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 always 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.

10.1.3 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 and by the Investigator. The study code, the title of the study, the progressive number and the date of the amendment must be recorded on the first page of the document. Exhaustive

justifications that motivate the amendment to the protocol should clearly be addressed in the document. All protocol amendments must be submitted to the IRB/EC for review and approval unless it covers administrative issues only. In this case, the IRB/EC will be notified of the amendment for information purposes only.

10.1.4 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 with the only exception when immediate changes are necessary to protect the safety, rights, and welfare of the subjects.

In order to obtain interpretable results, neither the Investigator nor the Sponsor/CRO 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 it to the CRO as soon as possible, in writing. In no instance should this increase the subject's risk or affect the validity of the study data.

10.1.5 Data collection

Electronic Case Report Forms (eCRFs) will be used for recording patient's study data using a validated web-based Electronic Data Capture (EDC) system. It is the responsibility of the Investigator to ensure that the eCRFs are properly and completely filled in. The eCRFs must be completed for all patients who have been included in the study.

Each authorized site personnel will be assigned a login and password to enter the EDC system via a secure network. Each login uniquely identifies the user and appropriate permissions will be set-up according to the user role. The access to the system will be granted once the user's training will be completed and documented.

Queries will be used to validate/clarify data entered on an eCRF page. Some queries will be generated automatically by the system when the user saves data that does not meet the criteria pre-defined for the data field. In addition, others will be created manually in the system and sent either by the study monitor (as result of Source Data Verification) or by Clinical Data Management.

Discrepancies raised will be reviewed online to determine the corrective action needed. Changes will be made directly by authorized site staff. The EDC system's audit trail will keep track of any information entered, modified and deleted. The audit trail will include, as a minimum, what was entered/changed/modified, who made the action and when the action was made. Any answered query will be reviewed and closed by authorized users. The Investigator will electronically sign the eCRF to validate the content.

Patient's source documentation (i.e., hospital charts) will be maintained at the clinic. Source data to be recorded directly onto the eCRFs will be communicated in advance. In cases where source documents are not eCRFs, the information on the eCRFs must match the source documents. Source data verification will be regularly performed by the blinded study monitor.

All the study questionnaires will be filled on electronic diary at the timepoints mentioned in the study flow chart. Data from study questionnaires will be then automatically transferred to EDC.

10.1.6 Monitoring and Quality Assurance

The study will be monitored by CRO's adequately qualified and trained clinical monitors on a regular basis throughout the study period to ensure the proper conduct of the clinical trial. The purposes of clinical trial monitoring are to verify that the rights and well-being of study patients are protected, that the reported trial data are accurate, complete and verifiable against the source documents, and that the study is conducted in accordance with the current protocol, Good Clinical Practice guideline and applicable regulatory requirements. During the monitoring visits, monitors will verify the following including, but not limited to, patient informed consent, patient's eligibility, safety data and reporting, quality of source documents and eCRF data against patient's medical records. If inconsistencies are identified, the corresponding corrections to the eCRF data will have to be made by the Investigator. Monitors will also check patient compliance, accrual, drug handling, including dispensing procedures and accountability logs, delegation of responsibilities within the Investigator's team, relevant communications with family doctors, if any, ancillary equipment and facilities, including refrigerators and freezers, local labs, etc. The Investigator and other site staff involved in the study must allocate enough time to the monitor at these visits.

Upon request by the Sponsor, or following the CRO's audit plan, on-site study audits may be conducted in order to ensure the study is in compliance with GCP, applicable regulatory requirements, and the study protocol. The auditing activities may also be conducted after study completion.

In addition, Regulatory Authorities may wish to conduct on-site inspections (during the study or after its completion). If a Regulatory Authority notifies the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the Investigator must inform the study Sponsor and CRO immediately. The Investigator will make all efforts to facilitate the conduct of the audits and inspections giving access to all necessary facilities, data and documents.

10.1.7 Study Documentation and Records retention

The medical (hospital) files of trial patients should be retained in accordance with national legislation (and in accordance with the maximum period of time permitted by the hospital (or institution/private practice).

The Sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/EC review, and regulatory inspection(s), providing direct access to source data/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 fifteen (15) 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) and ICH-GCP guidelines

[Reilly2013]. Should the Investigator wish to assign the study documentation to another party or move to another location, the Sponsor should promptly be notified.

10.1.8 Confidentiality

The Sponsor and the CRO must ensure that the Investigator keeps secret from third parties any confidential information disclosed or provided by the Sponsor and regarding the Sponsor and its study-related products. 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 with the CRO on behalf of the Sponsor.

10.1.9 Publication policy

Helsinn Healthcare SA is committed to public disclosure of research results that involve Helsinn products and for Helsinn sponsored publications, the International Committee if Medical Journal Editors (ICMJE) will apply to all named authors. As a general rule, the Sponsor and the Investigator(s) agree that no publications presenting or discussing data and/or results from clinical trials sponsored by Helsinn Healthcare SA will take place until the participating center(s) has/have completed the study, the data have been interpreted, and the final report has been issued. As a rule, the Sponsor is free to use the data collected in the sponsored study for the drug registration, world-wide scientific product documentation, and for publication.

The Sponsor shall have the sole and exclusive right to the first publication of the study data. Such Sponsor publication is intended to be a multi-center publication of the study data, collected from all investigators and institutions participating in the study. If the Investigator is interested in contributing to or participating in the Multi-Center Publication, he or she must contact the Sponsor. Selection of authors/participants will be governed by the Sponsor, considering individuals' contribution to the Study.

The Institution and the Investigator may publish or otherwise present the results of the Study Data obtained by the Institution and/or the Investigator provided that all of the following conditions have been satisfied: (i) the Multi-Center Publication has occurred; or, if no such publication has occurred, a manuscript should be submitted within 12 months of Study Drugs' first approval or within 18 months of the decision to discontinue Study Drugs' development, allowing for congress presentation first; (ii) before submitting the Independent Submission to a publisher, reviewer or other outside party, the Institution and/or the Investigator must submit the proposed Independent Submission to the Sponsor and allow the Sponsor at least sixty (60) days to review and provide comments; (iii) the Institution and/or the Investigator shall, as requested by the Sponsor, delete all references to Confidential Information (excepting the results of the Study obtained by the Institution and the Investigator); (iv) the Institution and the Investigator shall consider the Sponsor's comments and proposed revisions in good faith; and (v) if at any point during the initial sixty (60) day review the Sponsor so requests, the Institution and/or the Investigator shall delay the publication or presentation of the Independent Submission for up to sixty (60)

additional days in order to permit the Sponsor time to obtain Intellectual Property protections.

10.1.10 Insurance

The Sponsor/designee will obtain clinical study liability insurance, which covers health impairments resulting from drugs and/or substances/investigational products administered in the course of this study for which the patient has given his/her written informed consent.

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12 APPENDICES

APPENDIX 1: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCALE

ECOG Performance Status (To be rated by Investigator)

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

APPENDIX 2: BODY WEIGHT MEASUREMENTS-STUDY SPECIFIC PROCEDURES

Sites will be instructed to follow:

- Patient weighing for this study (Visit 1 to Visit 10) may only be performed by a Sponsor-trained and certified healthcare professional
- Body weight should be measured at each visit
- Calibrated scale dedicated for use in this study will be used every visit for the study, including for screening visits. Sponsor will make sure the same scale is used at each site.
- Scales will be used on hard flooring, such as tile, wood, or cement for accuracy
- Sites will be instructed to weigh the participants at approximately the same time of the day every visit, on empty stomach (in mornings before breakfast)
- Study participants will be instructed to void before getting on weighing scale
- Study participants will be instructed to remove shoes and clothing for accurate weight measurement. Patients will be weighed wearing only a hospital gown or hospital scrubs and, if desired, underwear only

APPENDIX 3: CYP3A4 INHIBITORS AND INDUCERS

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

Refer to the following website for a complete list:

http://medicine.iupui.edu/flockhart/table.htm

APPENDIX 4: FACIT MEASUREMENTS

The FACIT Measurement System is a collection of QOL questionnaires targeted to the management of chronic illness: "FACIT" (Functional Assessment of Chronic Illness Therapy). FACIT is a broader, more encompassing term that includes the FACT questionnaires. 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. For this study we plan to administer all four domains. The FAACT A/CS domain is a 12-item measure of patients' perceptions of anorexia/cachexia symptoms and concerns. The FACIT-F domain is a 13-item measure specifically to address the physical and functional consequences of fatigue [FACIT.org].

FACIT questionnaires are all formatted for self-administration, and use a 5-point Likert-type scale where patients rate each item from 0 to 4 (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very Much); the recall period for each question is "during the past 7 days".

FACT-G (Version 4)

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
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	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
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	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.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

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

	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
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FAACT (Version 4)

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
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

5-item-Anorexia Symptom Subscale consists of items C6, ACT3, ACT 6, ACT 7 and ACT10
4-item-Anorexia Concerns Subscale consists of items ACT 1, ACT 2, ACT 4 and ACT 9

FACIT-F (Version 4)

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

APPENDIX 5: SCORING GUIDELINES

FAACT Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FAACT).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB)	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	=PWB subscale score
SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	=SWB subscale score
EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____
				Sum individual item scores: _____	
				Multiply by 6: _____	
				Divide by number of items answered: _____	=EWB subscale score
FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	=FWB subscale score

FAACT scoring template 05.21.03

FAACT Scoring Guidelines (Version 4) – Page 2

Subscale	Item Code	Reverse item?		Item response	Item Score
ANOREXIA	C6	0	+	_____	=_____
CACHEXIA	ACT1	0	+	_____	=_____
SUBSCALE	ACT2	4	-	_____	=_____
(ACS)	ACT3	4	-	_____	=_____
	ACT4	4	-	_____	=_____
Score range: 0-48	ACT6	4	-	_____	=_____
	ACT7	4	-	_____	=_____
	ACT9	4	-	_____	=_____
	O2	4	-	_____	=_____
	ACT10	4	-	_____	=_____
	ACT11	4	-	_____	=_____
	ACT13	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 12: _____
Divide by number of items answered: _____=AC subscale score

To derive a FAACT Trial Outcome Index (TOI):
Score range: 0-104

_____ (PWB score) + _____ (FWB score) + _____ (ACS score) =_____=FAACT TOI

To Derive a FACT-G total score:
Score range: 0-108

_____ (PWB score) + _____ (SWB score) + _____ (EWB score) + _____ (FWB score) =_____=FACT-G Total score

To Derive a FAACT total score:
Score range: 0-156

_____ (PWB score) + _____ (SWB score) + _____ (EWB score) + _____ (FWB score) + _____ (ACS score) =_____=FAACT Total score

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

FAACT scoring template 05.21.03

Additionally, based on the Item codes of the here-above FAACT ACS, the following scores will be computed:
- 5-item Anorexia Symptom Subscale = C6+(4-ACT3)+(4-ACT6)+(4-ACT7)+(4-ACT10)
- 4-item Anorexia Concerns Subscale = ACT1+(4-ACT2)+(4-ACT4)+(4-ACT9)

FACIT-Fatigue Subscale Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE SUBSCALE	HI7	4	-	_____	=_____
	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered:

_____=**Fatigue Subscale score**

Additionally, based on the here-above Fatigue Subscale (FACIT-F), the Physical well-being and the Functional well-being, the FACIT-F TOI will be computed as:
FACIT-F TOI = FACIT-F + PWB + FWB.

APPENDIX 6: PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS) AND PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Patient Global Impression of Severity (PGIS)

Which of the following statements best describes your current appetite/eating-related symptoms? (*Please pick ONE box*)

☐ I currently do not have any appetite/eating-related symptoms

☐ I currently have minor appetite/eating-related symptoms

☐ I currently have moderate appetite/eating-related symptoms

☐ I currently have severe appetite/eating-related symptoms

Please choose the response below that best describes your current concerns about your weight. (*Please pick ONE box*)

☐ I have not had any concerns about my weight

☐ I have had minor concerns about my weight

☐ I have had moderate concerns about my weight

☐ I have had severe concerns about my weight

Patient Global Impression of Change (PGIC)

Since the start of the treatment, how would you describe your change in appetite/eating-related symptoms? (*Please pick ONE box*)

☐ Very much improved
☐ Much improved
☐ Minimally improved
☐ No change
☐ Minimally worse
☐ Much worse
☐ Very much worse

Since the start of treatment, how would you describe the change in how much you worry about your weight? (*Please pick ONE box*)

☐ Very much improved
☐ Much improved
☐ Minimally improved
☐ No change
☐ Minimally worse
☐ Much worse
☐ Very much worse

Since the start of the treatment, how would you describe your change in overall condition? (Please pick ONE box)

☐ Very much improved
☐ Much improved
☐ Minimally improved
☐ No change
☐ Minimally worse
☐ Much worse
☐ Very much worse

APPENDIX 7: HUNGER ASSESSMENT SCALE

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

I have felt hungry.	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
	0	1	2	3	4
My family and friends are pleased with my appetite.	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
	0	1	2	3	4

APPENDIX 8: NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

NYHA grading		MET*
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).	2–3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

*MET (metabolic equivalent) is defined as the resting ¥O for a 40-year-old 70kg man.1 MET₂= 3.5mL O /min/kg body weight.

Reproduced from: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines

Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated Oct 2011