Human Subjects Protocol

VA Puget Sound IRB

Pilot clinical trial of Macimorelin to assess safety and efficacy in patients with Cancer Cachexia

MIRB #00954

Funding Agency: VA/SIBCR

Principal Investigator: Jose Garcia

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Abstract

Every year, over 1.5 million individuals in the US are diagnosed with cancer. Cachexia, defined as an involuntary weight loss >5%, and anorexia (decreased food intake and appetite) are present in up to 80% of these patients, decreasing functional performance, quality of life (QOL) and survival. However, treatments for this condition are lacking. Feeding behavior is maintained by a network of interconnected brain areas, including the hypothalamus and striatum. The striatum signals the rewarding effects of food, while the hypothalamus responds to states such as hunger and satiety. The extent to which cancer cachexia and anorexia affect these circuits and their response to different interventions have not been characterized. In non-cancer models, administration of ghrelin or its mimetics decreases resting energy expenditure (EE) and inflammation and increases food intake and food reward. This leads to an increase in lean body mass (LBM) and fat mass. However, its role in cancer anorexia-cachexia syndrome (CACS) is not well-characterized. To study the pathways regulating appetite in this setting and the mechanisms mediating the effects of ghrelin mimetics on food intake and reward, we will perform functional Magnetic Resonance Imaging studies on cancer patients with cachexia before and after receiving the ghrelin mimetic macimorelin for 7 days. There are no published reports studying the different components of CACS in the human brain. We will assess its effects on hypothalamic and reward centers in the brain, and the effects of macimorelin on brain activity related to food intake.

Hypothesis: in CACS, compared to placebo, macimorelin will: a) increase appetite, food intake, and food reward, b) decrease REE and inflammation, c) improve QOL.

Specific aim: to determine the role of macimorelin on appetite, food intake, energy expenditure, inflammation, food reward, and QOL in CACS. In this double-blind, placebo-controlled trial, subjects with CACS will be randomized to placebo (N=2) v. macimorelin (N=6). Comparisons will be made between groups for changes from baseline in appetite (visual analogue scale), food intake (food diary and test meal), body weight, serum cytokines, REE (indirect calorimetry), food reward (fMRI), and QOL (questionnaires).

Significance: There is currently no effective therapy for CACS. This study will increase our understanding of the brain mechanisms mediating CACS, a necessary step in the development of effective therapies. These results are expected to open new avenues for treating symptoms associated with cancer and to improve QOL in this population. The present proposal will: **a)** Establish for the first time the extent to which abnormalities in food reward contribute to CACS in humans; **b)** Validate the use of fMRI in the study of cancer-related appetite regulation in humans which until now relies heavily in rodent data; and **c)** Establish the role of macimorelin in this setting and provide insight into its mechanisms of action by establishing the relative contribution of changes in food intake, food reward, and REE.

List of Abbreviations

AEZS	Æterna Zentaris
ALT	Alanine transaminase (SGPT)
ASAS	Anderson Symptom Assessment Scale
AST	Aspartate transaminase (SGOT)
BIA	Bioimpedance Analysis
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Panel
CO2	Carbon dioxide
CRP	C-Reactive Protein
CPRS	Computerized Patient Record System
CTCAE	Common Terminology Criteria for Adverse Events
DLDCC	Dan L. Duncan Cancer Center
DXA	Dual Energy X-Ray Absorptiometry
DMC	Data Monitoring Committee
DTI	Diffusion Tensor Imaging
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECG	Electrocardiogram
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FSH	*Follicle-Stimulating Hormone*

fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practices
GH	Growth Hormone
GHS-R	Growth Hormone Secretagogue Receptor
HbA_{1c}	Hemoglobin A_{1c}
hCG	*Human Chorionic Gonadotropin*
HGS	Handgrip strength
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity CRP
H&P	History and Physical
ICH	International Conference on Harmonization
IGF-1	Insulin-like growth factor-1
IGFBP-3	Insulin-like growth factor binding protein-3
IL-6	Interleukin-6
IRB	Institutional Review Board
ITT	Intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	Non-small cell lung cancer
NCI	National Cancer Institute
REE	Resting Energy Expenditure
RSFC	Resting State Functional Connectivity

SCP	Stair Climbing Power
USA	United States of America
VAS	Visual Analogue Scale
VCO2	maximal Carbon dioxide
VO2	maximal oxygen uptake

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1.0 Study Personnel

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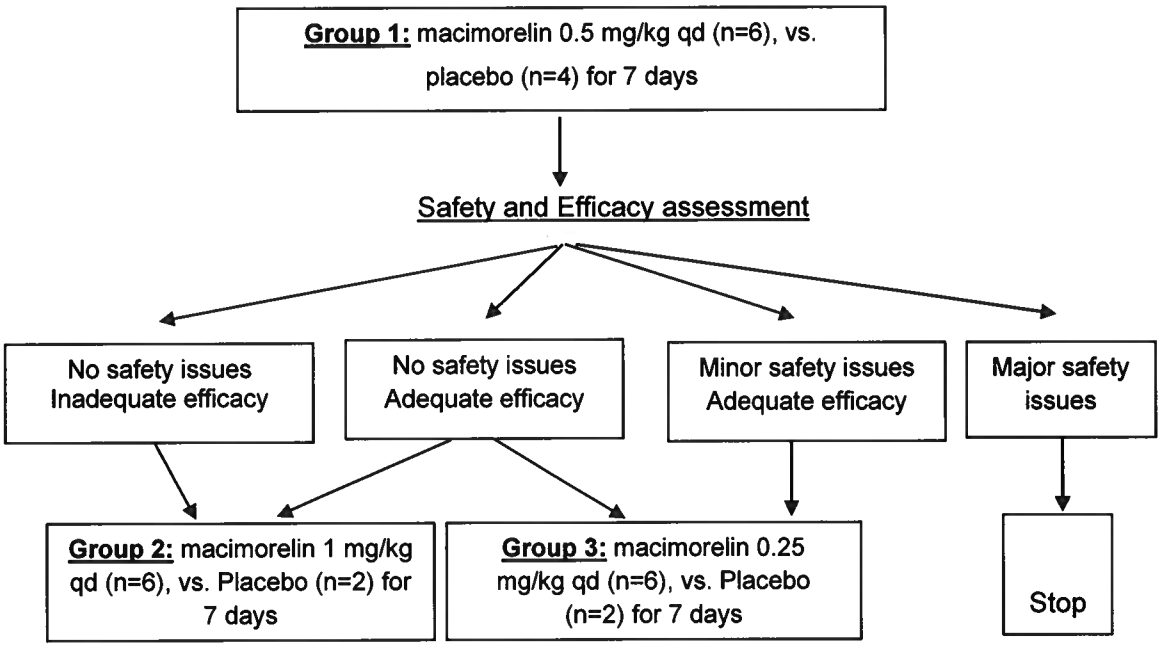
2.0 Introduction

2.1 Synopsis

This study is a continuation of a sequential protocol initiated at the Houston VA wherein safety and assessment of a daily, weeklong administration of an initial Macimorelin dose was assessed before proceeding with additional assessment of various doses. The following flow chart summarizes that study design:



Safety and efficacy of the Group 1 dose was completed while still an active protocol in Houston. It was determined that there were no safety issues but there was inadequate efficacy (defined as a ≥0.8 kg of body weight gain or a ≥50 ng/mL increase in plasma IGF-1 levels or an improvement in quality of life questionnaires of at least 15% compared to placebo). The protocol continued with Group 2 recruitment only. One patient completed the Group protocol before the study was moved with Dr. Garcia to the Puget Sound VA. Herein we submit the detailed protocol for continuation with Group 2 only. ***Note: placebo patients from Groups 1 (N=4) and 2 (N=2) will be combined for comparison to the Macimorelin group(s).*** A synopsis of the protocol is provided below.

Title	Pilot clinical trial of Macimorelin to assess safety and efficacy in patients with cancer cachexia
Principal Investigator/ Investigational Site/Sponsor	Jose M. Garcia, MD, PhD VA Puget Sound Health Care System Building 1, Room 815J

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Drug source/Medical Monitor	**Drug source:** Æterna Zentaris, Inc 50 Weismullerstrasse Frankfurt 60314 Germany **Medical Monitor:** Jose M. Garcia, MD, PhD VA Puget Sound Health Care System Building 1, Room 815J 1660 South Columbian Way (S-182-GRECC) Seattle, WA 98108-1597 Jg77@uw.edu Phone: (206) 764-2984 Fax: (206) 764-2569
Study Duration	November 2016-November 2017 (estimated)
Study Objectives	Primary Objectives: To evaluate the safety and efficacy of oral administration of macimorelin daily for 1 week in view of a development for the treatment of cachexia based using the following parameters: 1. Change of body weight (kg) between day 1 and day 7 2. Change of plasma IGF-1 between day 1 (prior to dose) and day 7 3. Change of quality of life score (ASAS, FACIT-F) between day 1 and day 7 Secondary Objectives: 1. Food intake as measured by a food diary to be recorded for 3 days before days 1 and 7 and by a test meal done at screening and on day 7. 2. Change of appetite measured by a validated visual analogue scale (VAS) between day 1 and day 7. 3. Body composition as measured by bio-impedance (BIA) and dual energy x-ray absorptiometry (DXA) on days 1 and 7. 4. Muscle strength as measured by handgrip strength (HGS) and stair climbing power (SCP). 5. Resting energy expenditure (REE) as measured by indirect calorimetry. 6. Change in IGFBP-3, GH, CRP, IL-6, TNF-α, and glucose between

	day 1 and day 7. 7. Changes in reward from food as measured by brain functional Magnetic Resonance Imaging (fMRI). 8. Changes in functional brain connectivity as assessed by Resting State Functional Connectivity (RSFC) imaging and Diffusion Tensor Imaging (DTI). <u>Safety Objectives:</u> 1. Clinical laboratory parameters: complete blood count (CBC), comprehensive metabolic panel (CMP), urinalysis (UA) 2. Vital signs, 3. Electrocardiogram (ECG) at days 1 and 7 before and 1 hour after dosing and on the post-study visit. 4. Recording of adverse events from day 1 to day 7 <u>Long-Term Objective:</u> The long-term objective of this research is to determine the extent to which the ghrelin mimetic macimorelin will affect energy intake and energy expenditure, and the effect that these changes will have on body weight, body composition, and functional performance in cancer patients with cachexia
Population	Approximately 8 patients with diagnosis of cancer induced cachexia (defined as a weight loss of ≥5% body weight in the 6 months prior to screening) will be randomized 3:1 to macimorelin vs. placebo.
Design	In this double-blind, placebo-controlled trial, patients will be randomized to: 1) placebo or 2) macimorelin given daily for 1 week. Safety and efficacy will be assessed at 1 week. Comparisons will be made for changes from baseline between groups.
Relevance	The present proposal will improve our understanding of symptoms that affect cancer patients. Collectively, these outcomes will establish the role of ghrelin mimetics in cancer cachexia and give us an insight into their mechanisms of action. This will improve quality of life and may open new avenues for the treatment of these symptoms. An improvement in functional performance is expected to allow patients to stay home longer, decreasing the need for hospitalizations and reducing the cost of healthcare.
Treatments	Patients will receive macimorelin (1mg/kg) or placebo (Powerade®) daily according to the protocol as stated in the 'study design' section.
Inclusion/Exclusion	Inclusion: 1. Patients ≥18 years of age with histological diagnosis of active solid or hematological malignancies 2. ECOG performance status of 0-2, 3. Presence of cancer-related cachexia defined as an involuntary weight loss of at least 5% of the pre-illness body weight over the

	previous 6 months, and 4. Provide written informed consent prior to screening. Exclusion: 1. Obesity (body weight >140 Kg); 2. Recent active excessive alcohol or illicit drug use; 3. Severe depression as determined by the investigator; 4. Other causes of cachexia such as: Liver disease (AST or ALT > 3x normal levels); renal failure (creatinine >1.5 mg/dL), untreated thyroid disease, class III-IV CHF, AIDS, severe COPD requiring home O_2; 5. Inability to increase food intake (e.g., esophageal obstruction, intractable nausea and vomiting); 6. Any condition that would prevent the patient from performing the research procedures (e.g. unstable coronary artery disease); 7. Use of growth hormone, megestrol, Marinol, or any other anabolic agents, appetite stimulants, tube feeding, or parenteral nutrition during the 1 month prior to entering the study. 8. Systemic corticosteroids administration for > 6 days a month (i.e. daily continuous schedule). 9. Recent administration (less than 1 week) of highly emetogenic chemotherapy (Hesketh scale class 4-5); patients may otherwise be undergoing chemotherapy. 10. Being female and pregnant, breast-feeding or of childbearing potential. (Note: Lack of childbearing potential for female patients is satisfied by: a) being post-menopausal; b) being surgically sterile; c) practicing contraception with an oral contraceptive, intra-uterine device, diaphragm, or condom with spermicide for the duration of the study; or d) being sexually inactive. Confirmation that the patient is not pregnant will be established by a negative urine hCG pregnancy test at the time of enrollment. 11. Co-administration of drugs that prolong QT interval (Appendix II), CYP3A4 inducers (Appendix III), QTc equal to greater than 450ms at screening or other investigational agents (a wash-out period of five times the half-life of drugs that prolong QT will be allowed with approval of prescriber). 12. Conditions that would preclude from successfully scanning patients in MRI: a. Claustrophobia (this would make lying in the scanner very uncomfortable); b. having a pacemaker, aneurysm clips, neurostimulators, cochlear implants, metal in eyes, steel worker, or other implants; c. History of Seizures, d. History of head injuries resulting in loss of consciousness > 10 minutes.
Statistics	This is a pilot and exploratory study to assess safety and efficacy. The data generated through this trial will be used to power a future,

	larger clinical trial. All efficacy variables will be summarized descriptively by treatment using N, mean, SEM, and standard deviation. Data from placebo-receiving patients from all groups will be pooled together for the purpose of analyses since their treatment will be identical. Analyses will be done as changes from baseline using paired t-test for continuous variables and Fisher's exact test for categorical variables. Also, one-way ANOVA will be used to compare the differences in outcomes between groups. Appropriate transformations will be applied to the outcome changes to improve distribution toward normality. As recommended by the CONSORT guidelines (1), we will develop both completers and intention-to-treat models. We have selected primary endpoints for each specific aim based on the clinical relevance of each outcome and the research questions proposed. Other endpoints will be considered secondary endpoints that will provide supplemental evidence to the conclusions drawn from these primary variables or will explore different areas. Full disclosure and complete description of all endpoints will be included in public presentations of data to avoid bias. Safety, including adverse events, ECGs, vital signs, and laboratory assessments will be summarized descriptively by treatment group. Analysis of fMRI data will be as follows: We use a general linear model in analyzing and designing our fMRI experiments. To compare data from different patients, the scan data from each patient must be transformed into a standard anatomical framework. We follow the approach of Frackowiak et al (1997), which analyzes the brain into small local volumes, or "voxels." The fMRI signal from each voxel is then subjected to the following transformation and analysis steps: Analysis Step 1: Spatio-temporal normalization to a standard brain map, and smoothing to improve the signal to noise ratio. Analysis Step 2: Statistical analysis to determine the significance of the activity measured at each voxel. We use an established statistical framework (2, 3) in terms of a general linear model, which incorporates and formalizes the independent explanatory variables in our experiment. Given the variance of each parameter, we can construct a t-statistic as a measure of the significance of differences in the parameters estimated from different experiments, at different voxels, or in different patients. In practice, we construct a t-statistic out of a particular linear combination of the parameters that describes a

	quantity of interest. To express this mathematically, we define a contrast vector that specifies a linear combination of parameters. Then the t-statistic is the quantity of interest divided by its standard error. When we calculate a t-statistic at each voxel in an imaged brain, measuring the significance of a difference between parameters from different patients or different experimental conditions, the resulting set is called a statistical parametric map. We use such maps to determine areas of significant activation in the brain during presentation of stimuli or performance of the task. DTI analysis will be performed using the TrackVis software.
Data Monitoring Committee	The Data Monitoring Committee (DMC) will perform data monitoring on a regular basis, but at least annually. Study progress and enrollment, toxicities, adverse events, risk-to-benefit ratio, and soundness of study data, as well as other factors that can affect study outcome will be evaluated. DMC monitoring will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

2.2 Overview of Target Condition: Cancer Cachexia

Over 1,500,000 new diagnoses of cancer are made in the U.S. every year (4). In most cases, this condition will have a great impact in the individuals' survival and quality of life (QOL). Cachexia (a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass (5)) is very common in patients with cancer (6). It contributes to a decrease in functional performance, takes a heavy toll on patients' quality of life and is associated with poor survival (7).

Unlike what is seen in diet-induced weight loss, cancer cachexia patients have diminished appetite, food intake and insulin sensitivity (8). We and others have found several abnormalities in different hormonal axes regulating appetite and body weight in this setting and they have been postulated to have a pathogenic role. These include abnormalities in growth hormone/insulin-like growth factor-1 (GH/IGF-1), gonadal axis, inflammation and appetite regulating peptides including ghrelin, leptin and other adipokines (9-12).

Despite the significant burden that cachexia and other cancer-related symptoms such as anorexia and poor functional status represent to cancer patients, these symptoms often remain undiagnosed and untreated. Moreover, there are currently no approved treatments for cancer-related cachexia and off-label treatments used for this condition such as appetite stimulants (e.g., megestrol acetate) are largely ineffective and are associated with potentially serious side effects (i.e., adrenal insufficiency, hypogonadism, deep venous thrombosis, etc.).

2.3 Anorexia and its contribution to cancer-cachexia

Up to 80% of patients with advanced cancer experience a decrease in appetite and food intake (13). This is caused by the tumor itself since it is present even in treatment-naïve patients but it is usually worsened by the administration of emetogenic chemotherapy or radiotherapy (14). Other factors that may play a role include neuropsychiatric factors such as depression or pain, gastrointestinal obstruction and alterations in taste (15). This decrease in appetite takes a toll in these patients' quality of life and deeply affects the family's perspective on the disease.

The etiology of cancer cachexia and anorexia is not well-understood. We hypothesize that the brain must play a major role because a) the hypothalamus is the control center for energy homeostasis in the body and b) the striatum is the reward center that determines how appetitive a particular food feels. To study the pathways regulating appetite in the setting of cancer cachexia and anorexia, we will perform functional Magnetic Resonance Imaging (fMRI) studies on cancer cachexia patients. There are no published reports studying the different components of cancer cachexia and anorexia in the human brain. We will assess the effects of cancer cachexia and anorexia on hypothalamic signaling and on reward centers in the brain. We will also study the effects of the novel ghrelin mimetic (GHS) macimorelin on brain activity related to food intake.

2.4 Ghrelin and Food Reward

A widely accepted view of feeding behavior states that it is controlled mainly by a homeostatic element (gut peptides that work at the hypothalamic level) and hedonic signals based in the striatum (16). In healthy humans, ghrelin acts both at the hypothalamic and at the striatal levels (17) favoring food reward, the intake of palatable food, to increase preference for caloric foods, and motivated behavior for food (18). Nothing is known about the brain effects of ghrelin or ghrelin mimetics on brain activity during cancer cachexia and anorexia, or the effects of this syndrome on the reward system in the brain.

2.5 Safety of Ghrelin in the Setting of Cancer

As with all clinical trials, the issue of safety is our first priority. The GHS-R is expressed in many normal and tumor tissues including breast, thyroid and prostate and in-vitro studies have given conflicting results (19)(20). Administration of a growth factor such as ghrelin or GH to tumor-bearing individuals raises potential concerns of stimulation of tumor growth, particularly through elevation of IGF-1. However, when whole animal tumor growth studies have been conducted to evaluate the effect of increasing GH tone, the results have generally indicated a beneficial effect (21-23). There have been publications implicating IGF-1 in oncogenic potential; in addition, there have been reports indicating the therapeutic potential of the major binding protein, IGFBP-3, in attenuating oncogenic behavior either via its ability to bind IGF-1 or via direct, IGF-independent actions. Consequently, it may be that the balanced effect of a growth hormone based intervention

to increase both IGF-1 and IGFBP-3 may be responsible, in part, for some of the apparent discrepancies. Hanada et al.(24) tested the effects of ghrelin in a different model of tumor-induced cachexia. In this experiment, cachexia was reversed by the administration of ghrelin and tumor size remained unchanged, decreasing the tumor/carcass ratio. The composite preclinical literature indicates beneficial effects of ghrelin-based intervention in cancer-related weight loss models; it increases lean body mass and in some studies reduces disease progression relative to the untreated state.

More importantly, administration of ghrelin mimetics was well-tolerated and safe in preliminary studies where approximately 40 patients with cancer-induced cachexia were exposed for at least 3 months (25). Consequently, the overall conclusion from these preclinical and clinical in-vivo evaluations is the likelihood that activation of GHS-R will support and improve host function without producing detrimental effects on the underlying malignancy.

2.6 Rationale for Macimorelin Administration in Cancer Cachexia

Macimorelin is an orally active ghrelin mimetic and growth hormone secretagogue. Ghrelin is the endogenous ligand for the growth hormone secretagogue receptor (AKA ghrelin receptor, GHS-R) (26, 27). Pharmacological treatment of rats and mice with ghrelin stimulates food intake and increases body weight (28). Also, ghrelin reduces fat oxidation and increases adiposity (29). Smith et al. have shown that *Ghsr -/-* mice are refractory to the stimulatory effects of ghrelin on GH release and appetite, confirming that the GHSR-1a is a physiologically relevant ghrelin receptor (30).

Activation of GHSR-1a by ghrelin mimetics (growth hormone secretagogues, GHS) also induces GH secretion (31) and it increases food intake and body weight (32, 33). In non-cancer patients, ghrelin mimetics increase body weight and reverse the negative nitrogen balance induced by starvation independently of their orexigenic effects. These findings suggest that ghrelin's effects are not entirely mediated through an increase in appetite and that other mechanisms, such as a decrease in energy expenditure, are involved (34). Ghrelin administration decreases energy expenditure in non-cancer human and animal models (35, 36). In two small groups of cancer patients, a single infusion of ghrelin was well tolerated, increasing appetite and food intake in one of the studies (9) but not in the other (37).

Because ghrelin is a peptide with a half-life of 30 minutes, its efficacy in humans is limited unless it is administered parenterally as a continuous infusion. Ghrelin mimetics such as macimorelin are non-peptidic, orally available, small molecules that have a relatively long half-life allowing for once-a-day administration. These compounds have been in clinical trials for over a decade and our group and others have demonstrated their safety and efficacy (33, 38).

2.7 Summary of Clinical Experience with Macimorelin

Macimorelin is a synthetic pseudotripeptide with GHS activity similar to ghrelin. This compound is currently in clinical trials as a diagnostic agent for the investigation of suspected AGHD irrespective of the cause being at the hypothalamic or pituitary level.

In toxicological studies, no organ toxicities could be identified after oral or intravenous dosing. Toxicities were only observed after intravenous dosing with resulting extremely high plasma levels. Toxico-kinetic data indicated that the majority of the toxicity findings were observed at plasma levels which are about 1000 times higher as compared to the anticipated human exposure. All findings after intravenous dosing were considered to be irrelevant for oral dosing.

Dose recommendations for clinical use have been established for oral administration based on PK and PD studies conducted in healthy volunteers. Macimorelin has been given to about 100 people (52 patients with AGHD and 48 healthy subjects without GHD). The most frequent common adverse reaction after macimorelin was dysgeusia, a distortion of the sense of taste, reported by 12 test persons, diarrhea reported by 3 persons, and 7 other types of possible reactions in 1 person each. Macimorelin has been reported to have likely caused one serious side effect in one subject to date. An electrocardiogram that was recorded 60 minutes after macimorelin administration indicated that the subject could be experiencing abnormal heart rhythm, although the subject was experiencing no symptoms. The subject was hospitalized and a series of tests were run that all indicated the subject's heart was normal. The next day, the abnormalities seen in the electrocardiogram the previous day were no longer present and the subject was discharged from the hospital. In a recent trial with 28 healthy volunteers, macimorelin was dosed up to 4 times higher than in our current research study. Macimorelin was well tolerated up to the highest dose. One out of six subjects after macimorelin 0.5 mg reported dizziness and upset stomach. Four out of 15 subjects reported possible adverse reactions after higher doses of macimorelin. The adverse reactions included 3 episodes of headache and one episode each of dizziness and diarrhea.

Macimorelin is metabolized mainly by CYP3A4 but has no CYP3A4 inhibitory activity. Therefore, macimorelin is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors or inducers of CYP3A4 may affect the pharmacokinetic profile of macimorelin. Co-administration of potent CYP3A4 inhibitors or inducers should be avoided. Please see the Investigators Brochure for the complete background on this drug.

3.0 Objectives

3.1 Primary Objective

To evaluate the safety and efficacy of repeated daily oral administration of macimorelin at different doses for 1 week in view of a development for the treatment of cachexia based using the following parameters:

1. Change of body weight (kg) between day 1 and day 7
2. Change of IGF-1 plasma levels between day 1 (prior to dosing) and day 7
3. Change of quality of life score (Anderson Symptom Assessment Scale, FACIT-F) between day 1 and day 7

Hypothesis: One week administration of Macimorelin will be well tolerated and will improve body weight, plasma IGF-1, and quality of life compared to one week administration of placebo in patients with cancer cachexia.

3.2 Secondary Objectives

1. Food intake as measured by a food diary to be recorded for three days before days 1 and 7 and by a test meal done at screening and on day 7
2. Change of appetite measured by a validated visual analogue scale (VAS) between screening and day 7
3. Body composition as measured by bio-impedance analysis (BIA) and dual energy x-ray absorptiometry (DXA) on days 1 and 7
4. Muscle strength as measured by handgrip strength (HGS) and stair climbing power (SCP)
5. Resting energy expenditure (REE) as measured by indirect calorimetry
6. Change in systemic blood parameters (GH, IGFBP-3, CRP, IL-6, TNF-α, and glucose) between day 1 and day 7
7. Changes in reward from food as measured by brain functional Magnetic Resonance Imaging (fMRI)
8. Changes in functional brain connectivity as assessed by Resting State Functional Connectivity (RSFC) imaging and Diffusion Tensor Imaging (DTI)

Hypothesis: One week administration of Macimorelin will improve food intake, appetite, body composition, HGS, SCP, REE, systemic blood parameters, reward from food, and functional brain connectivity compared to one week administration of placebo in patients with cancer cachexia.

3.3 Safety Objectives

1. Clinical laboratory parameters: CBC, CMP, UA
2. Vital signs
3. ECG changes at day 1, day 7 and post-study visit
4. Recording of adverse events from day 1 to day 7

Hypothesis: One week administration of Macimorelin will be well tolerated with no serious adverse events in patients with cancer cachexia.

4.0 Resources and Personnel

Research procedures will be conducted within the VAPSHCS at Dr. Garcia's dedicated research spaces and at the Clinical Research Unit (CRU). Dr. Garcia will oversee all study procedures including recruitment, consenting, administering surveys, data analysis, and coordination of all regulatory activities. Approved study staff (i.e. research nurses, postdoctoral fellows, study coordinators) will also carry out these procedures under the supervision of Dr. Garcia. Dr. Garcia and approved study staff will have access to protected health information. CRU staff may be contracted to perform study procedures in the case of an approved study staff member being unavailable. CRU staff will not have access to protected health information.

5.0 Study Procedures

5.1 Study Design

This is a double-blind, randomized, placebo-controlled trial to test the effects of the ghrelin mimetic macimorelin in cancer-cachexia patients after one week of administration. Adequate efficacy will be defined as a ≥0.8 kg of body weight gain or a ≥50 ng/mL increase in plasma IGF-1 levels or an improvement in quality of life questionnaires of at least 15% compared to placebo. The timeline of the study procedures are as follows:

	Screening: Day -24 to Day -1	Baseline: Day 1	Day 7: assessment/end of treatment	Post-study visit: 14 +/- 3 days after end-of-treatment
Informed Consent	X			
History and exam[1]	X	X	X	X
AEZS-130 administration		X	X	
PD[2]		X	X	
ECG and Safety Labs[3]	X	X	X	X
Body Composition Analyses[4]		X	X	

Functional performance assessment[5]		X	X	
Resting energy expenditure[6]		X	X	
Questionnaires[7]		X	X	
Laboratory assays[8]		X	X	
Appetite and food intake assessment[9]	X		X	
MRI	X		X[10]	
Adverse Events		X[10]	X	X

Footnotes: Patients will receive treatment daily between days 1 and 7. Dosing on days 1 and 7 will take place in the clinic. Patients will take the drug at home on days 2-6. All tests will be done before dosing unless otherwise noted.
[1] Exam will include body weight measurement and a complete physical exam.
[2] Pharmacodynamics (PD) will be assessed before and 1 hour after dosing with measurements of GH.
[3]Safety labs will include: CBC with Diff, comprehensive metabolic panel, and UA (including hCG for females). On days 1 and 7 ECG will be performed before and 1h after dosing.
[4]Tests include bioimpedance analysis and dual energy x-ray absorptiometry.
[5]Functional performance will be assessed by: a) handgrip strength, b) stair climbing power, c) activity level
[6]Resting energy expenditure will be assessed by indirect calorimetry.
[7]Questionnaires will include: The Eastern Cooperative Oncology Group (ECOG), and Karnofsky Scales, Anderson Symptom Assessment Scale (ASAS) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).
[8] This will include measurements of glucose, IGF-1, GH, IGFBP-3, IL-6, CRP, and TNF-alpha.
[9] Appetite will be assessed by a VAS before and 1h after breakfast; food intake will be assessed by a food diary. A test meal will be given at screening and 1h after dosing on day 7.
[10]After dosing

Upon completion of the Day 1 procedures, allowing for procedure exemptions where applicable, the subject will be paid $100 by check. Upon completion of the Day 7 procedures, allowing for procedure exemptions where applicable, the subject will be paid an additional $100 by check.

5.2 Study Drug

Study drug (Macimorelin) will be provided at no cost by Æterna Zentaris (AEZS). The Pharmaceutical Development group from AEZS has analyzed the stability of macimorelin in Powerade® for 7 days at both room temperature (25°C) and at 2-8°C. Data indicate that if stored refrigerated (2-8C), the solution is stable over 7 days whereas at room temperature (25°C) it should not be stored longer than 3 days. Due to those results, macimorelin mixed in Powerade® and Powerade® alone will be prepared in individual doses by the MEDVAMC research pharmacy. Patients will receive macimorelin 1 mg/kg and matching placebo (Powerade®) according to the protocol as stated above in the 'study design' section. The study staff (PI, pharmacist, or authorized study coordinator) will dispense the product to the patients. On day 1 and 7, patients will be dosed at the clinical research center by the coordinator. From days 2 through 6, patients will self-administer the drug or placebo at home. Patients will be instructed to keep these doses in the refrigerator at 2-8°C and to drink them while fasting at least 1 hour before breakfast.

5.3 Blinding

The allocation schedule will be stored securely; no member of the investigational team involved in generation or review of the study database will be allowed to see the allocation schedule or data that may otherwise unblind treatment allocations. Two sealed envelopes will be kept for each patient. One will be kept in the Research Pharmacy and the other in the patient's file in case a patient needs to be unblinded. Unblinding should be avoided to the extent possible. Unblinding should only occur in emergencies for which knowledge of the treatment allocation will affect patient care decision-making. Formal unblinding of the study will occur after the database is locked or if requested by the DMC.

5.4 Drug Inventory and Disposition

An exact inventory of all study drug(s), including placebo, will be maintained at the investigational site. The study drug(s) will be stored in a locked storage area under environmental conditions appropriate for the product(s). All study drug(s) will be accounted for. Study drug(s) will only be shipped or destroyed upon written authorization from AEZS.

5.5 Screening Visit

- Screening evaluations will be performed within three weeks prior to the baseline visit and may occur on different days. Informed consent must be obtained prior to any screening procedures.
- Informed consent will be scanned and entered into our electronic medical records (CPRS) as per current VA guidelines.
- Following signature of informed consent, participants will be given a study ID using the format: [protocol#].[enrollment#]
- After signing the informed consent and review of inclusion and exclusion criteria, a complete history and physical exam (H&P) will be performed. Special emphasis will be placed on evaluation for any signs of pedal edema, pleural effusions, and ascites. Body weight will be obtained on a calibrated scale dedicated for this study. Patients will remove shoes, belts, wallets, keys, and cell phones. Underwear and a gown will be worn.
- A fasting blood sample (30 mL) will be obtained to measure safety labs including a complete blood count with differential (CBC with Differential), and comprehensive metabolic panel, and a UA (including hCG for females).
- An ECG also will be performed.
- Instructions and training for the proper use of the food diary will be given during the screening visit. Patients meeting the I/E criteria will be provided a 3-day food diary to assess food intake 3 days prior to their baseline visit.

- Selection of breakfast menu options: The patient will be asked to indicate his/her food preferences from several breakfast menu options for the test meal to be served at screening and again at the week 1 visit. The identical meal options will be provided on both days. A surplus of food will be provided so that availability of food does not limit caloric consumption.

- After informed consent but before the test meal is given, patients' brains will be imaged in a Phillips 3T scanner. Before starting the experiment, an investigator or trained technician will give the patient instructions on the safety of the MRI scan. The MRI scanner we will use differs from conventional scanners only in that the magnet strength is 3.0 T, rather than the more typical 1.5 T magnets used in routine clinical scanning. The patient will enter a large room where a powerful magnet is located. Patient will be instructed to remove all jewelry and other metal-containing objects. The patient will then be placed on a narrow table with plastic-encased metal coil close to the head. Next, the patient will be slid into a small tunnel approximately 6 feet long and 25 inches in diameter. The duration of the scan is approximately 30 minutes. A small mirror will be positioned above the patient's head so the other end of the scanner is visible. After the patient is positioned, the table will move the patient into the scanner itself. The patient will be in voice-communication with a technician or investigator via an intercom, and will have access to a squeeze bulb that generates a loud noise just in case the patient would like to be withdrawn at any point. Each patient will undergo two scanning sessions (pre and Day7 macimorelin or placebo). A computer display will be positioned at one end of the scanner and can be seen through the mirror above the patient's head. Patients will be asked to allow us to put one or two small, soft, rubber tubes, similar to straws, into his/her mouth. The tubes will be used to give patient small squirts of a flavored beverage while in the scanner. Patients will simply swallow, while keeping his or her head still. Patients will be given a CD with .gif images of their brain taken during the structural scan if it is their first time being scanned.

- Breakfast Test Meal: The breakfast test meal "calorie count" will be conducted to assess the effect of study drug on stimulating food intake. Precise source documents will be maintained recording every food item consumed during the breakfast test meal as well as the date, start time of food consumed and the quantity of food consumed. In order to ensure accuracy, the serving plate and every food item will be weighed in advance of serving. The remaining food items and plate will then be re-weighed and the weight subtracted from the original weight measured before the meal was served. It is essential that a surplus of food is offered so that availability of food does not limit caloric consumption. Calories for unit-dose foods (e.g., a carton of milk) will be derived from the product label; for other foods and beverages, calories will be calculated from a standardized software package. Appetite will be assessed by a VAS before and 1h after breakfast.

- Patients will be instructed to refrain from physical activity the day before testing on days 1 and 7 to avoid changes in REE that can be induced by exercise.

- All Information will be entered into Case Report Forms (CRF).

5.6 Day 1 Visit

- A complete history and physical exam will be performed. Special emphasis will be placed on evaluation for any signs of pedal edema, pleural effusions, and ascites. Body weight will be obtained on a calibrated scale dedicated for this study as indicated above. Patients will remove shoes, belts, wallets, keys, cell phones and any heavy clothing i.e. sweaters or sweatshirts. Underwear and a gown will be worn.

- A fasting blood sample will be obtained before dosing to measure CBC with Differential, comprehensive metabolic panel, glucose, IGF-1, GH, IGFBP-3, IL-6, CRP, and TNF-alpha and a UA (including hCG for females). A growth hormone level will be measured again 1 hour after dosing. An aliquot of the sample will be stored for up to 5 years after the study is completed to measure other inflammatory and anabolic markers.

- ECGs will be performed before dosing and again 1 hour after dosing.

- REE will be assessed by indirect calorimetry before dosing. Briefly, patients will rest in a supine position for at least 30 min before undergoing indirect calorimetry using a ventilated hood technique. This system provides measurements of VO_2 and VCO_2, which have an error of less than 4% (39). This method is termed 'indirect' as the method of collection of gas is from a transparent hood placed over the head of the patient. One end of this hood is connected to the indirect calorimeter to measure CO_2 and O_2 content in the expired air. Air is drawn in from the other end of the tube, from which a portion is sampled to measure CO_2 and O_2 in the inspired air. Measurements were performed for at least 30 minutes. The measurements performed in the last 20 minutes will be averaged to calculate REE using the Weir equation (40). This method is currently considered one of the 'gold standard' methods to assess energy expenditure. Respiratory quotient (VCO_2/VO_2 ratio, RQ) will also be calculated as a measure of relative utilization of carbohydrates and fat.

- Body composition will be measured by BIA and DXA before dosing. BIA is a noninvasive method of estimating body composition based on the ability of tissues to conduct an electrical current. Based on this principle, lean tissue conducts electricity better than fat; therefore, the body composition analyzer/scale is able to calculate total body water, total body fat and total body lean mass. DXA scan uses a low amount of radiation to determine fat mass and bone mass and calculates fat-free mass (whole body and segmental).

- Functional performance will be assessed before dosing by: a) HGS and b) SCP. These tests have been shown to correlate with VO_2 max and are good tests of aerobic and functional capacity in cachectic states (41, 42). Briefly, HGS will be measured by a handheld dynamometer (Jamar Hydraulic Dynamometer, J.A. Preston Corp., Clifton, NJ) as described elsewhere (43). SCP, which allows measuring the

maximal anaerobic power of the involved muscles, will be performed as follows. At the moment of the first execution, 2–3 practice trials will be allowed so that the patients gained a good control of the performing technique. SCP consists in a modification of the test proposed by Margaria et al, (44), recently applied in elderly patients (45). In brief, patients will be invited to climb up ordinary stairs at the highest possible speed, according to their capabilities. The stairs will consist of 13 steps of 15.3 cm each, thus covering a total vertical distance of 1.99 m. An experimenter will measure the time employed to cover the test with a digital stopwatch. In line with Margaria et al. (44), assumptions, anaerobic power (in W) will be calculated by using the following formula: "body mass x 9.81 x vertical distance/time where body mass, vertical distance (i.e., 1.99 m) and time are expressed in kg, m and s, respectively, and 9.81 m/s^2 represents the acceleration of gravity. Physical activity will be monitored from Day 1 to Day 7 with the Actical Version 3.0 activity monitor (Respironics Inc., Murrysville, PA). The wrist-worn monitor will be provided on Day 1, along with verbal instructions for proper use, and worn for the entire 7-day study period until it is returned to study staff on the Day 7 visit.

- Previously validated questionnaires including the ECOG and Karnofsky scales will be administered. Patients will also complete the ASAS and FACIT-F questionnaires to assess changes in symptoms that play a role in performance such as fatigue.

- Food diary will be retrieved and information entered into the CRF. A new food diary will be given and patients asked to complete it 3 days before the next visit.

- Patients will be randomized as indicated above to placebo or macimorelin. All patients will receive the first dose before being discharged. Patients will be instructed to keep the drug in the refrigerator at 2-8° C and to take the drug on an empty stomach in the morning at least 1 h before breakfast, because it was previously demonstrated that the administration of macimorelin with food significantly reduced its GH secretagogue efficiency and bioavailability. The research Pharmacy will provide each patient with 5 syringes (days 2 through 6) with either Powerade® alone (placebo) or macimorelin diluted in the same volume of Powerade®. Patients will be also provided with a bag and asked to return the empty syringes for drug accountability.

- Patients will be asked to refrain from physical activity the day before the next visit to avoid changes in REE that can be induced by exercise. Patients will be asked not to take the dose of study drug the day of the Day 7 visit.

- All Information will be entered into CRFs.

5.7 Day 7 Visit

- The Actical activity monitor will be returned to study staff at the beginning of this visit.

- A complete history and physical exam will be performed as indicated above. Special emphasis will be placed on evaluation for AEs and any signs of pedal edema, pleural effusions, and ascites. Body weight will be obtained on calibrated scale dedicated for this study as indicated above. Patients will remove shoes, belts, wallets, keys, cell phones and any heavy clothing i.e. sweaters or sweatshirts. Underwear and a gown will be worn.

- A fasting blood sample will be obtained before dosing to measure CBC with Differential, comprehensive metabolic panel, glucose, IGF-1, GH, IGFBP-3, IL-6, CRP, and TNF-alpha and UA (including hCG for females). A growth hormone level will be measured again 1 hour after dosing. An aliquot of the sample will be stored for up to 5 years after the study is completed to measure other inflammatory and anabolic markers.

- ECGs will be performed before dosing and again 1 hour after dosing.

- REE, BIA, DXA, HGS, and SCP will be assessed as indicated above.

- Questionnaires including the ECOG and Karnofsky scales will be administered. Patients will also complete the ASAS and FACIT-F questionnaires to assess changes in symptoms that play a role in performance such as fatigue. Patients will receive at this time the study drug dose.

- A new MRI session (equal to the one on Screening Visit) will be administered approximately 45 minutes after dosing but before the test meal.

- Breakfast Test Meal will be provided 1.5 hours after dosing with the same items and amount provided at the screening visit. Appetite will be assessed by a VAS before and 1h after breakfast. Food diary will also be retrieved at this visit.

- Blood samples for GH measurements will be obtained 1h after dosing.

- Drug accountability will be assessed by counting the number of empty syringes that the patient returned.

- All Information will be entered into CRFs.

5.8 Post-Study Visit

- An H&P will be repeated by the PI with special emphasis on AEs. A fasting blood sample will be collected as previously described for measurement of safety labs including CBC with Diff, comprehensive metabolic panel, hCG (for females), UA. An ECG will be performed.

5.9 Recruitment Methods

Eight total participants who complete the entire protocol are needed. Participants will be recruited from the Oncology clinic through our collaborator Dr. Wu and his clinical staff as follows:

- Study staff accesses medical records to identify potential participants from oncology clinic
- Study staff reviews records to ascertain initial inclusion/exclusion criteria
- Study staff sends list of potential participants to clinical staff
- Clinical staff brings up potential research study to patient at clinical visit and asks if they're interested in learning more
- Study staff then speaks with patients to provide more information
- If patient is interested they sign a consent form
- Screening/baseline visit occurs

5.10 Informed Consent Procedure

- The PI and his staff will consent patients. Patients will be identified through analysis of electronic medical records at the VAPSHCS by our collaborator, the Oncologists, and the research staff. Patients will be approached by study staff at their cancer clinic after clinical staff brings up potential research study to patient at clinical visit and asks if they're interested in learning more. Patients are offered the informed consent form for consideration of volunteering for the study. Staff will explain the study to patients, providing a signed copy of the consent for their records. Patients will be assured of the voluntary nature of the trial and a member of the research staff will be available to answer all questions regarding the study. We will emphasize that their decision to participate in the clinical trial will not affect their treatment.

- A waiver of consent is requested for identification/screening. The use or disclosure of protected health information involves no more than minimal risk to the individuals and the waiver will not adversely affect the privacy rights and the welfare of the individuals. The risk is minimal because: 1) only trained personnel will have access to this information, 2) information will be accessed only from our research office at the VA and kept in a locked cabinet behind locked doors or in password-protected computers and 3) only information absolutely required for research will be obtained and recorded (full medical history, name, date of birth, and last 4 numbers of the SSN).The research could not practicably be conducted without this waiver and could not practicably be conducted without access to and use of the protected health information because accessing potential patients' medical records and their last 4 digits of their SSN and name is required to approach them to explain the proposed research and consent them.

- An adequate plan exists in order to protect health information (PHI) identifiers from improper use and disclosure to minimize the risk of loss of confidentiality as recommended by VA guidelines. Adequate written assurances exist in order to ensure

that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule to minimize the risk of loss of confidentiality as recommended by VA guidelines.

- Study personnel will be trained regarding human subjects' protections requirements and how to obtain and document informed consent as it is required by local and Federal VA guidelines. All study documents containing PHI will be kept in a locked cabinet inside a locked room. No data containing PHI will be accessible outside the study site. The room is kept locked with the door shut. No patient data is left out of the cabinets. Confidential information will be stored on servers managed and maintained by the VA-IT program. All computers are password protected.

- Sub-investigators will be provided the participant study number and de-identified (all 18 HIPAA identifiers will be removed prior to sending data outside the VA) study data for analysis. No sensitive information will be share and the data will be transferred electronically via secure email. No social security numbers will be requested from patients or potential patients via phone.

- The PI, VA collaborators, research staff, and VA research compliance monitors will have access to identifiable information. People who ensure quality from the institutions where the research is being done, federal and other regulatory agencies will have access to all of the research data. No else will have access to identifiable research data. An Accounting of Disclosure (AOD) will be created and maintained for any disclosure of individually identifiable information (III) outside the VA. The manual spreadsheet will include the date of the disclosure, nature or description of the III disclosed, purpose of each disclosure and the name and address of person or agency to which the disclosure was made.

5.11 Inclusion/Exclusion Criteria

5.11.1 Inclusion Criteria

1. Patients ≥18 years of age with histological diagnosis of active solid or hematological malignancies

2. ECOG performance status of 0-2,

3. Presence of cancer-related cachexia defined as an involuntary weight loss of at least 5% over the previous 6 months, 10% over the previous 12 months or 2% over the previous 6 months with a BMI<20, and

4. Provide written informed consent prior to screening.

5.11.2 Exclusion Criteria

1. Obesity (body weight >140 Kg);

2. Recent active excessive alcohol or illicit drug use;

3. Severe depression as determined by the investigator;

4. Other causes of cachexia such as: Liver disease (AST or ALT > 3x normal levels); renal failure (creatinine > 1.5 mg/dL), untreated thyroid disease, class III-IV CHF, AIDS, severe COPD requiring use of home O_2;

5. Inability to increase food intake (e.g., esophageal obstruction, intractable nausea and vomiting);

6. Any condition that would prevent the patient from performing the research procedures (e.g., unstable coronary artery disease);

7. Use of growth hormone, megestrol, Marinol, or any other anabolic agents, appetite stimulants, tube feeding, or parenteral nutrition during the 1 month prior to entering the study;

8. Systemic corticosteroids administration for > 6 days a month (i.e.daily continuous schedule).

9. Recent administration (less than 1 week) of highly emetogenic chemotherapy (Hesketh scale class 4-5); patients may otherwise be undergoing chemotherapy.

10. Being female and pregnant, breast-feeding or of childbearing potential. (Note: Lack of childbearing potential for female patients is satisfied by: a) being post-menopausal; b) being surgically sterile; c) practicing contraception with an oral contraceptive, intra-uterine device, diaphragm, or condom with spermicide for the duration of the study; or d) being sexually inactive. Confirmation that the patient is not pregnant will be established by a negative urine hCG pregnancy test at the time of enrollment.

11. Co-administration of drugs that prolong QT interval (Appendix II), CYP3A4 inducers (Appendix III), QTc equal to greater than 450ms at screening or other investigational agents (a wash-out period of five times the half-life of drugs that prolong QT will be allowed with approval of prescriber).

12. Conditions that would preclude from successfully scanning patients in MRI: a. Claustrophobia (this would make lying in the scanner very uncomfortable); b. having a pacemaker, aneurysm clips, neurostimulators, cochlear implants, metal in eyes, steel worker, or other implants; c. History of Seizures; d. History of head injuries resulting in loss of consciousness > 10 minutes.

5.12 Study Evaluations

5.12.1 Quality of Life Measures

The study will include the following patient-reported Quality of Life Instruments: ASAS and FACIT-F. These instruments have been previously used and validated in clinical research investigations. These instruments must be completed by the patient before other procedures are done at follow-up visits. When the patient has completed the questionnaires, the forms will be collected from the patient and entered into the case report forms (CRFs) by authorized site personnel. Site personnel should review the forms to ensure all questions were answered and that the intended answers were clearly marked before the patient leaves the study site. 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 any or all of the questions, the reason must be documented in the source documentation and in the CRF.

5.12.2 Cardiac Assessment

Cardiac assessment includes a 12-lead ECG test. Electrocardiogram testing will be performed on all patients. ECG will be performed during the post-study visit.

5.12.3 Laboratory Assessments

All hematology, blood chemistries, urinalysis, serum/urine pregnancy tests (if applicable) will be performed by the local laboratory at the investigational site.

5.12.4 Handgrip Strength Testing

HGS determination will be performed using a hand-held dynamometer. On each occasion that HGS is measured, the measurement will be made three times for each hand: 3 measurements for the right hand, followed by 3 measurements for the left hand. A rest period of at least 30 seconds will take place between each individual measurement. During measurement of HGS, the participant should be asked to remove any jewelry that would prevent him/her from exerting maximum squeezing force with either hand. Patient is seated on a chair with feet flat on the floor and facing table/desk. Patient holds dynamometer vertically, supported by table/desk, with elbow flexed approx. 90°. Patient will squeeze the dynamometer with the maximum force for up to four seconds, during which time the administrator says "Squeeze as hard as you can!" and, as patient squeezes "harder!...harder!", and "relax."

5.12.5 Body Composition

Weight will be measured using the calibrated scale dedicated for use in this study. This and all other weights will be collected with the patient wearing only a hospital gown or hospital scrubs (and, if desired, underwear). Patients must be barefoot when weighed. All weights will be recorded in kilograms. Values collected using other scales or other procedures (e.g., while wearing heavy clothing) are prohibited for the purpose of this trial.

BIA and DXA will be performed in an effort to gain insight into the practicality of this methodology and to gain insight into the relationship of body weight changes relative to body composition changes. BIA is a noninvasive method of estimating body composition based on the ability of tissues to conduct an electrical current. Based on this principle, lean tissue conducts electricity better than fat; therefore, the body composition analyzer/scale is able to calculate total body water, total body fat and total body lean mass. DXA scan uses a low amount of radiation to determine fat mass and bone mass and calculates fat-free mass (whole body and segmental).

5.12.6 Biomarkers

Serum samples for all biomarker determination (IL-6, TNF-α, CRP, GH, IGF-1, IGFBP-3) will be drawn and processed at the research site lab.

5.12.7 Physician-Reported Instruments

Patients will be evaluated for performance using the Eastern Cooperative Oncology Group (ECOG), and Karnofsky Scales, at each visit (see Appendices II and III).

5.12.8 Indirect Calorimetry

Resting energy expenditure will be measured by indirect calorimetry. Following an overnight fast, patients will rest in a supine position for at least 30 min before undergoing indirect calorimetry using a ventilated hood technique. This method is termed 'indirect' as the method of collection of gas is from a transparent hood placed over the head of the patient. One end of this hood is connected to the indirect calorimeter to measure carbon dioxide and oxygen content in the expired air, and air is drawn in from the other end of the tube, from which a portion is sampled to measure oxygen and carbon dioxide in the inspired air.

Measurements will be performed for at least 30 min. The measurements performed in the last 20 min will be averaged to calculate REE using the Weir equation (40). This method is currently considered one of the 'gold standard' methods to assess energy expenditure. Respiratory quotient (VCO_2 /VO_2 ratio, RQ) will be calculated as a measure of relative utilization of carbohydrates and fat.

5.12.9 Stair Climbing Power

The patients will be instructed to ascend a standard flight of stairs as quickly as possible, using the handrail if necessary. Time will be recorded to the nearest 0.01 second. The power is calculated in watts by dividing the time elapsed into the product of the body weight, the vertical distance, and the acceleration of gravity (9.8 m/sec·sec).

5.12.10 Laboratory assays

Serum samples for all biomarker determination (IL-6, TNF-α, GH, IGF-1, IGFBP-3) will be drawn and processed at the research site lab.

5.12.11 Test Meal

Food intake will be measured as a secondary outcome by a free-choice test meal and a food diary. After signing an informed consent, trained personnel will instruct patients on the use of the food diary, review food preferences and perform the food intake analysis. Based on this information, patients will be given free access to food items of their like and instructed to eat as much as they want. This procedure will take place at screening after signing informed consent and review of I/E criteria and on day 7 one (1) hour after dosing. The same food items and amounts will be provided at each meal. Food items will be weighed before and after each test meal and total calories as well as the relative proportion of fat, carbohydrates (CHO) and protein will be measured using FoodWorks version 7.01 (TNC, Long Valley NJ, USA). Changes from baseline in Kcal, fat, CHO and protein consumed will be measured and placebo-treated patients will serve as controls.

We will use a food diary detailing intake for 3 consecutive days (including 1 weekend day and 2 weekdays) to assess patients' nutrient intake and eating patterns. This method has been shown to adequately reflect current dietary intake in this population (2). This diary consists of 6 fields to be completed each day, corresponding to 3 main meals (breakfast, lunch, and dinner) and 3 between-meal snacks (morning, afternoon, and evening). Trained personnel will instruct participants on completion of the food record and later review the records with each participant for accuracy and completeness. Each patient will be asked to complete this diary the week before starting treatment and again three days before the Day 7 visit. Analysis will be done using FoodWorks version 7.01 and will focus on energy intake and the percentage of total energy contributions (% of kcal) from fat, carbohydrate, and protein. Mean intake will be expressed per person per day and per kg of body weight. Mean changes from baseline will be compared between patients randomized to Macimorelin vs. placebo.

5.12.12 Imaging

Imaging will be performed with a 3-Tesla Phillips MRI located at the University of Washington. Patients will lay still for ~30 min in the scanner. The only instruction is that they should swallow little squirts of juice (0.8 ml, just enough to taste the juice) several times, while keeping eyes open and being as still as possible. Imaging data will be analyzed separately for fMRI, DTI and DSFC. Correlations between different imaging modalities and between imaging data and behavioral and physiological measures will be used to extract meaningful biological data.

5.12.13 Data Analysis

5.12.13.1 Statistical Analyses

This is a pilot and exploratory study to assess safety and efficacy. The data generated through this trial will be used to power a future, larger clinical trial. All efficacy variables will be summarized descriptively by treatment using N, mean, SEM and standard deviation. Data from placebo-receiving patients from all groups will be pooled together for the purpose of analyses since their treatment will be identical. Analyses will be done as changes from baseline using paired t-test for continuous variables and Fisher's exact test for categorical variables. Also, one-way ANOVA will be used to compare the differences in outcomes between groups. Appropriate transformations will be applied to the outcome changes to improve distribution toward normality. As recommended by the CONSORT guidelines (1), we will develop both completers and intention-to-treat (ITT) models.

We have selected primary endpoints for each specific aim based on the clinical relevance of each outcome and the research questions proposed. Other endpoints will be considered secondary endpoints that will provide supplemental evidence to the conclusions drawn from these primary variables or will explore different areas. Full disclosure and complete description of all endpoints will be included in public presentations of data to avoid bias. Safety, including adverse events, ECGs, vital signs, and laboratory assessments will be summarized descriptively by treatment group.

Analysis of fMRI data will be as follows: We use a general linear model in analyzing and designing our fMRI experiments. To compare data from different patients, the scan data from each patient must be transformed into a standard anatomical framework. We follow the approach of Frackowiak et al (46) which analyzes the brain into small local volumes, or "voxels." The fMRI signal from each voxel is then subjected to the following transformation and analysis steps:

-Analysis Step 1: Spatio-temporal normalization to a standard brain map, and smoothing to improve the signal to noise ratio.

-Analysis Step 2: Statistical analysis to determine the significance of the activity measured at each voxel. We use an established statistical framework (2, 3) in terms of a general linear model, which incorporates and formalizes the independent explanatory variables in our experiment.

Given the variance of each parameter, we can construct a t-statistic as a measure of the significance of differences in the parameters estimated from different experiments, at different voxels, or in different patients. In practice, we construct a t-statistic out of a particular linear combination of the parameters that describes a quantity of interest. To express this mathematically, we define a contrast vector that specifies a linear combination of parameters. Then the t-statistic is the quantity of interest divided by its standard error. When we calculate a t-statistic at each voxel in an imaged brain, measuring the significance of a difference between parameters from different patients or different experimental conditions, the resulting set is called a statistical parametric map. We use such maps to determine areas of significant activation in the brain during presentation of stimuli or performance of the task. DTI analysis will be performed using the TrackVis software.

5.12.13.2 Study Endpoints

Primary efficacy parameters:

- Change of body weight (kg) between day 1 and day 7
- Change of IGF-1 plasma levels between day 1 (prior to dose) and day 7
- Change of quality of life score (Anderson Symptom Assessment Scale, FACIT-F) between day 1 and day 7

Secondary efficacy parameters:

- Food intake as measured by a food diary to be recorded for 3 days before days 1 and 7 and by a test meal administered at screening and on day 7.
- Change of appetite measured by a validated visual analogue scale between day 1 and day 7.
- Body composition as measured by bio-impedance on days 1 and 7.
- Muscle strength as measured by handgrip strength and stair climbing power.
- Energy expenditure as measured by indirect calorimetry.

- Change in GH, IGFBP-3, CRP, IL-6 and TNF-α and glucose between day 1 and day 7.
- Changes in reward from food as measured by brain functional Magnetic Resonance Imaging (fMRI).
- Changes in functional brain connectivity as assessed by Resting State Functional Connectivity (RSFC) imaging and Diffusion Tensor Imaging (DTI).

Safety parameters:

- Clinical laboratory parameters: complete blood count (CBC), comprehensive metabolic panel (CMP), urinalysis (UA)
- Vital signs,
- Electrocardiogram (ECG) changes pre and post-dosing at day 1 and day 7 and on the post-study visit.
- Recording of adverse events from day 1 to day 7

5.12.13.3 Statistical Analyses

Safety, including adverse events, ECGs, vital signs, and laboratory assessments will be summarized by treatment group. All safety analyses will be performed on the ITT population. For continuous variables, descriptive statistics including the number of observations (N), mean, standard deviation, minimum, and the maximum will be presented for the values as well as for the change from baseline by treatment group at each time point. Treatment-emergent adverse events (TEAEs) are defined as those adverse events that start on or after the first dose of randomized study drug. The number and percent of patients reporting TEAEs, grouped by MedDRA system organ class and preferred term, will be tabulated by treatment group. Summaries will also be provided by maximum severity for the number and percentage of patients with TEAEs and for patients with drug-related TEAEs by system organ class, preferred term, and treatment group. Serious adverse events and adverse events leading to discontinuation will be summarized in a similar fashion. Vital signs at each time point and changes from baseline will be summarized by treatment group. Laboratory results of interest will be summarized by treatment group using frequencies and percentages. MRI has been repeatedly shown to be extremely safe. In fact, there is no reason to believe that the scanners can cause any undesirable effect. Safety precautions, however, are very important. The scanners are very strong electromagnets and any piece of metal inside the scanner room could potentially be a hazard. We are equipped with metal detectors (both in the room's door and wand style) and extensively query patients about the possibility of metals inside their bodies (pins, staples, etc).

5.12.14 Withdrawal of Participants

It is unlikely that participants will be withdrawn without their consent. This may happen if the sponsor or regulatory authorities (VA) decide to terminate the study. Participation is completely voluntary and patients may withdraw from this study at any time without any negative consequences or penalty for study withdrawal. To withdraw, patients will be instructed to advise study staff directly by calling the number in the consent form. The participant will not have the option to get the remaining portion of their sample back. Samples will not be destroyed but the sample will be kept anonymously and used for analysis. Patients may withdraw their consent and discontinue at any time with verbal or written notification to the investigators. Patients will be encouraged to complete the final endpoint and post-study visit procedures if possible.

6.0 Reporting

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study. The investigator will grade adverse events using the NCI-CTCAE, Version 4 (Appendix I). All adverse events occurring after any administration of the study drug through the 16 day post-treatment follow-up visit will be followed until the event resolves, until the patient begins alternative. However, certain adverse events (e.g., a cerebrovascular accident, worsening hypertension) will not be expected to resolve completely; in these cases, the date and time should be recorded when the event reaches its new, stable equilibrium and any remaining residua of the event should be documented.

The investigator is required to document all adverse events occurring during the clinical trial, commencing with the first dose of study drug through the 16 day post-treatment follow-up visit. Adverse events occurring following the signature of the informed consent, but prior to the first dose of study drug will not be reported as adverse events, but will be captured as medical history. The adverse event reporting period also ends if the patient begins an alternative therapy within 16 days of the last administration of study drug. It is also important to record all adverse events that result in permanent discontinuation of Macimorelin, whether serious or non-serious. All serious adverse events will be reported within 24 hours of study staff being made aware of the event, to AEZS. All serious adverse events will be reported within 7 calendar days of study staff being made aware of the event to FDA for fatal or life-threatening events and within 15 calendar days of study staff being make aware of the event to FDA for all other serious adverse events. Serious adverse events will also be reported within 5 business days of study staff being made aware of the event to IRB per posted guidelines (immediate oral notification will be made to IRB in the case of local death). The DMC will be notified via secured email according to the same regulations as reporting to IRB.

Any untoward or unfavorable event occurring following administration of study drug, whether or not it is considered to be related to the study drug will be considered an adverse event (AE). An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. All AEs, including observed or volunteered

problems, complaints, or symptoms, are to be entered into the paper CRFs. Each AE is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors. A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for serious AEs. A worsening of a pre-existing condition will be considered an AE as well. A pre-existing condition which occurs with a known temporal frequency and severity (e.g., dysmenorrhea) following drug exposure will not be considered an adverse event unless the pattern or severity has changed.

Patients should be instructed to report any AE that they experience to the Investigator. The investigator should assess for AE at each visit. AEs occurring during the clinical trial and the follow-up period should be recorded. To capture the most potentially relevant safety information during a clinical trial, it is important that the investigator record accurate AE terms on the paper CRFs.

Whenever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event.

- Seriousness: A serious adverse event (SAE) is any AE that: results in death, permanent or significant disability, hospitalization or a prolongation of an existing hospitalization; is a congenital anomaly/birth defect; or is otherwise medically alarming.

- Severity: All adverse events will be rated according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTCAE v4.0, Appendix I).

- Relationship to Study Drug: All adverse events will be assessed by the Investigator to establish the presumed causal relationship with the study drug considering: a) Temporal relationship, b) Pattern consistent with known drug effect and c) Presence of other potential etiologies. Adverse events will be assigned one of the following causal relationships:

    - Unrelated: The study drug almost certainly (or certainly) did not cause the event. Guidelines: There is no reasonable temporal relationship of the event to the administration of drug; the pattern is inconsistent with that known for the drug; and/or there is another obvious etiology.

    - Probably not related: It is more likely that the event is due to another etiology than due to the study drug. Guidelines: There is no reasonable temporal relationship of the event to the administration of drug; the pattern is inconsistent with that known for the drug; and/or there is another more likely etiology.

    - Possibly Related: It is equally likely that the event is due to the study drug as it is due to another etiology. Guidelines: There is a reasonable temporal relationship of the event to the study drug; the drug seems as likely as other etiologies to have caused the effect.

- Probably Related: It is more likely that the event is due to the study drug than due to another etiology. Guidelines: There is a reasonable temporal relationship of the event to the study drug; the event may be consistent with a known pattern of drug (or drug class) effects; the drug seems more likely than other etiologies to cause the effect; the adverse event diminished upon cessation of study drug exposure or reduction in dose; and/or the adverse event worsened or recurred upon unintentional re-exposure to the study drug (Intentional rechallenge for the purpose of assigning causality should not be performed).

- Definitely Related: The evidence is compelling that the study drug caused the adverse event. Guidelines: there is a reasonable temporal relationship of the event to the study drug; the event is consistent with a known pattern of drug (or drug class) effects; the drug is far more likely than other etiologies to have caused the effect; the adverse event diminished upon cessation of study drug exposure or reduction in dose; the adverse event worsened or recurred upon unintentional re-exposure to the study drug (Intentional rechallenge for the purpose of assigning causality should not be performed).

- Unknown: The data are inadequate to assign any of the above causal relationship categories to the study drug.

- Monitoring Adverse Events: Patients will be monitored for the onset of AEs throughout the course of the study from the time of first exposure to the study drug until the post-study visit. Any ongoing AE will be assessed at appropriate frequency to document the date and time of resolution of the event. All events will be followed to resolution even if ongoing at the post-study visit. Certain AEs (e.g., a cerebrovascular accident) will not be expected to resolve completely; in these cases, the date and time will be recorded when the event reaches its new, stable equilibrium and any remaining residua of the event will be documented. All AEs will be followed until resolution or until stable in cases where permanent sequelae are expected.

- Serious Adverse Event Reporting: A SAE (per 21 CFR §312.32) is any adverse experience occurring at any dose that results in any of the following outcomes:
  - Death
  - A life-threatening adverse drug experience
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant disability/incapacity
  - A congenital anomaly/birth defect

  All serious adverse events will be reported within 24 hours of study staff being made aware of the event, to AEZS. All serious adverse events will be reported within 7 calendar days of study staff being made aware of the event to FDA for fatal or life-threatening events and within 15 calendar days of study staff being make aware of the event to FDA for all other serious adverse events. Serious adverse events will also be reported within 5 business days of study staff being made aware of the event to IRB per posted guidelines

(immediate oral notification will be made to IRB in the case of local death). The DMC will be notified via secured email according to the same regulations as reporting to IRB. This reporting requirement is mandatory regardless of whether the event is considered to be drug related or not.

Important medical events may be considered an SAE based upon appropriate medical judgment. They may jeopardize the patient(s) and may require medical or surgical intervention to prevent one of the outcomes listed above. For all SAEs occurring during the study or within 16 days of the last administration of study drug, the Investigator must submit follow-up reports to AEZS or its representative regarding the status of the SAE and the patient's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the patient receives alternative therapy, or the patient dies. Follow-up reporting is done by faxing in SAE follow up reports.

AEZS must also be notified of any patient who becomes pregnant or their partner who becomes pregnant, while participating in a clinical trial. The Investigator must immediately notify the IRB and AEZS of any pregnancy associated with study medication exposure (at least 6 half-lives after drug administration) and record the event. Protocol-required procedures for study discontinuation must be performed on the patient unless contraindicated by pregnancy. All pregnancies must be followed to conclusion to determine their outcome. Infants should be followed for a minimum of 8 weeks.

7.0 Privacy and Confidentiality

Data collected in this VA research study, including identifiers will be maintained for at least 15 years by the VA facility. All study documents containing PHI will be kept in a locked cabinet inside a locked room. No data containing PHI will be accessible outside the study site. The room is kept locked with the door shut. No patient data is left out of the cabinets. Confidential information will be stored on servers managed and maintained by the VA-IT program. All computers are password protected. Sub-investigators will be provided the patient study number and de-identified (all 18 HIPAA identifiers will be removed prior to sending data outside the VA) study data for analysis. No sensitive information will be share and the data will be transferred electronically via secure email. No social security numbers will be requested from patients or potential patients via phone. AA0048 is the room number for the room in Health Sciences at UW Medical Center Disc Lab where the server for MRI data and physical MRI screening forms will be held; MRI data will be held on an encrypted server located at UW

8.0 Information Security and Data Storage/Movement

Source documents are the records maintained that represent the first written or electronic record of patient information. Source documents include signed informed consent forms, written progress notes, laboratory reports, ECG tracings, etc. All source documents must be maintained in the secured laboratory or office space. Source documents should be recorded in blue or black ink. Any corrections should be made by a single line drawn through the entry, adding the correct

information, initialing and dating by the person making the change, and (preferably) indicating why the change was required.

Paper case report forms will be used for this study. The Investigator will ensure that all data are captured on the CRFs promptly, completely, accurately, and conform to source documents. All CRFs will be kept with the corresponding source documents in separate patient files maintained in the secured laboratory or office space. CRFs will be transposed into electronic databases to be stored on the appropriate secured drive at the VA.

Regulatory agencies require retention of study records for 15 years following the termination of all clinical activities with the study drug or 15 years following approval of the product for marketing. Since the investigator may not be aware of the date when a product is approved or withdrawn, all study-related records, including all source documents and all case report forms must be maintained for at least 15 years.

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APPENDIX I: NCI-CTCAE, VERSION 4

The Revised National Cancer Institute Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, Version 4 may be viewed online at: http://ctep.cancer.gov/reporting/ctc.html

APPENDIX II: DRUGS THAT PROLONG THE QT INTERVAL

http://www.azcert.org/advisory-committee.cfm

Generic Name/ Name Class/Clinical Use Comments

Clomipramine Anafranil® Tricyclic Antidepressant / depression

Trimethoprim

Sulfa Bactrim® Antibiotic / bacterial infection

Diphenhydramine Benadryl® Antihistamine / Allergic rhinitis, insomnia

Citalopram Celexa® Anti-depressant / depression

Ciprofloxacin Cipro® Antibiotic / bacterial infection

Trazodone Desyrel® Anti-depressant / Depression,insomnia

Fluconazole Diflucan® Anti-fungal / fungal infection

Amitriptyline Elavil® Tricyclic Antidepressant / depression

Ketoconazole Nizoral® Anti-fungal / fungal infection

Imipramine Norfranil® Tricyclic Antidepressant / depression

Ritonavir Norvir® Protease inhibitor! HIV

Diphenhydramine Nytol® Antihistamine / Allergic rhinitis, insomnia

Nortriptyline Pamelor® Tricyclic Antidepressant / depression

Paroxetine Paxil® Anti-depressant / depression

Desipramine Pertofrane® Tricyclic Antidepressant / depression

Fluoxetine Prozac® Anti-depressant / depression

Galantamine Reminyl® Cholinesterase inhibitor / Dementia, Alzheimer's

Fluoxetine Sarafem® Anti-depressant / depression

Doxepin Sinequan® Tricyclic Antidepressant / depression

Itraconazole Sporanox® Anti-fungal / fungal infection

Trimethoprim

Sulfa Sulfa® Antibiotic / bacterial infection

Trimipramine Surmontil® Tricyclic Antidepressant / depression

muscarinic receptor

Solifenacin VESIcare® anatagonist I treatment of overactive bladder

Protriptyline Vivactil® Tricyclic Antidepressant / depression

Sertraline Zoloft® Anti-depressant / depression

Escitalopram Cipralex® Anti-depressantJ Maor depression! Anxiety disorders

Dolasetron Anzemet® Anti-nausea / nausea, vomiting

Moxifloxacin Avelox® Antibiotic / bacterial infection

Nicardipine Cardene® Anti-hypertensive / high blood pressure

Fosphenytoin Cerebyx® Anti-convulsant! seizure

Clozapine Clozaril® Anti-psychotic /schizoprirenia

Perflutren lipid Definity® Imaging contrast agent! microspheres Echocardiography

Isradipine Dynacirc® Anti-hypertensive / high blood pressure

Venlafaxine Etfexor® Anti-depressant I depression

Lithium Eskalith® Anti-mania / bipolar disorder

Gemifloxacin Factive® Antibiotic! bacterial infection

Felbamate Felbatrol® Anti-convulsant! seizure

Ofloxacin Floxin® Antibiotic! bacterial infection

Foscarnet Foscavir® Anti-viral / HIV infection

Ziprasidone Geodon® Anti-psychotic/schizophrenia

Paliperidone Invega® Antipsychotic, atypical! Schizophrenia

Telithromycin Ketek® Antibiotic / bacterial infection

Granisetron Kytril® Anti-nausea! nausea and vomiting

Levofloxacin Levaquin® Antibiotic! bacterial infection

Vardenafil Levitra® phosphodiesterase inhibitor!

Vasodilator

Escitalopram Lexapro® Anti-depressantJ Ma or depression/ Anxiety disorders

Lithium Lithobid® Anti-mania! bipolar disorder

Indapamide Lozol® Diuretic! stimulate urine & salt loss

Dronedarone Multaq® Anti-arrhythmic! Atrial Fibrillation

Chloral hydrate Noctec® Sedative! sedation/insomnia

Tamoxifen Nolvadex® Anti-cancer / breast cancer

Oxytocin Pitocin® Oxytocic! Labor stimulation

Tacrolimus Prograf® Immunosuppressant! Immune suppression

Ranolazine Ranexa® Anti-anginal/ chronic angina

Atazanavir Reyataz® Protease inhibitor! HIV

Chloroquine Aralen® Anti-malarial / malaria infection

Sotalol Betapace® Anti-arrhythmic / abnormal Females>Males heart rhythm

Clarithromycin Biaxin® Antibiotic / bacterial infection

Quinidine Cardioquin® Anti-arrhythmic / abnormal Females>Males heart rhythm

Amiodarone Cordarone® Anti-arrhythmic / abnormal Females>Males, TdP risk heart rhythm regarded as low

Ibutilide Corvert® Anti-arrhvthmic / abnormal Females>Males heart rhythm

Methadone Dolophine® Onapricaoteticagdoenpiesntdlepnacien control, Females>Males Antibiotic;GI stimulant /

Erythromycin E. E.S.® bacterial infection; increase Females>Males GI motility, Antibiotic; GI stimulant

Erythromycin Erythrocin® bacterial infection; increase Females>Males GI motility when given intravenously or at higher-than

Haloperidol Haldol® Anti-psychotic I recommended doses, risk schizophrenia, agitation of sudden death, QT prolongation and torsades increases.

Halofantrine Halfan® Anti-malarial / malaria infection Females>Males

Astemizole Hismanal® Arhnintiihtiisstamine / Allergic No Longer available in U.S.

Droperidol Inapsine® Sedative;Anti-nausea / anesthesia adjunct, nausea

Probucol Lorelco® Antilipemic /Hypercholesterolemia No longer available in U.S.

Thioridazine Mellaril® Anti-psychotic I schizophrenia

Methadone Methadose® Opiate agonist / pain control, Females>Males narcotic dependence

Domperidone Motilium® Anti-nausea / nausea Not available in the U.S.

Pentamidine NebuPent® Apnnetiu-minofencitaive / pneumocystis Females>Males

Disopyramide Norpace® Anti-arrhythmic / abnormal Females>Males heart rhythm

Pimozide Orap® tAicnsti-psychotic / Tourettes Females>Males

Levomethadyl Orlaam® Opiate agonist I pain control, narcotic dependence

Amiodarone Pacerone® Anti-arrhythmic / abnormal Females>Males,TdP risk heart rhythm regarded as low

Pentamidine Pentam® Apnnetiu-minofencitaive / pneumocystis Females>Males

Procainamide Procan® Anti-arrhvthmic / abnormal heart rhythm

Procainamide Pronestyl® Anti-arrhythmic / abnormal heart rhythm

Cisapride Propulsid® GI stimulant / heartburn Restricted availability; Females>Males.

Quinidine Quinaglute® Anti-arrhythmic / abnormal Females>Males heart rhythm

Terfenadine Seldane® Antihistamine I Allergic No longer available in U.S. rhinitis

Mesoridazine Serentil® Anti-psychotic / schizophrenia

Chiorpromazine Thorazine® Anti-psychotic? Anti-emetic /schizophrenia) nausea

Dofetilide Tikosyn® Anti-arrhythmic / abnormal heart rhythm

Arsenic trioxide Trisenox® Anti-cancer / Leukemia

Bepridil Vascor® Anti-anginal / heart pain Females>Males

Sparfioxacin Zagam® Antibiotic / bacterial infection

APPENDIX III: DRUGS THAT INDUCE CYP3A4

CYP3A4 inducers which are considered to be clinically relevant are: carbamazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone Avasimibe, Bosentan, efavirenz, etravirine, modafinil, nafcillin, Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, rufinamide