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TELEHEART: Telotristat Ethyl in a Heart Biomarker Study

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TELEHEART: Telotristat Ethyl in a Heart Biomarker Study

PI: Cezar Iliescu, MD

Department of Cardiology

The University of Texas, MD Anderson

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1.0 TITLE OF PROPOSED PROJECT: TELEHEART: Telotristat Ethyl in a Heart Biomarker Study

TOTAL PROJECT DURATION: 56 months

EXPECTED START DATE: estimated to be 1/1/2021

EXPECTED FINISH DATE: estimated to be 8/31/2025

2.0 Objectives

The purpose of the study is to evaluate the effect of telotristat ethyl (XERMELO) + somatostatin analog (SSA) (Treatment arm) versus placebo + SSA (standard of care arm) in patients with carcinoid syndrome and carcinoid heart disease. The study will be conducted in agreement with Good Clinical Practice guidelines and the Declaration of Helsinki and be submitted for approval to the MD Anderson Cancer Center IRB before initiation.

Primary Objective:

1. To estimate the percent change in NT-proBNP at 6 month visit from baseline after initiation of study drug in each arm and to compare the percent change between the two study arms.

Secondary Objectives:

1. To evaluate the change in functional capacity from baseline at 3 and 6 month visits as assessed by a 6 minute walk test (6MWT) in each arm
2. To evaluate changes in echocardiographic parameters (CVHD score, global longitudinal myocardial strain assessment of the Left and right ventricle/TAPSE) from baseline to 3 and 6 month visits in each arm
    a. Carcinoid Valvular Heart Disease (CVHD) score is determined by 1) tricuspid valve appearance, 2) tricuspid regurgitation severity by either spectral pulsed wave or color Doppler flow mapping; 3) pulmonary stenosis severity by spectral pulsed or continuous wave Doppler, and 4) pulmonary insufficiency severity by color Doppler. (Denney et al. JACC 1998)
    b. Global longitudinal myocardial strain assessment will be conducted using GE Vivid echocardiography machines in all studies. Significant change will be defined as a change in global longitudinal strain by 15%.
    c. TAPSE will be defined as normal (≥ 1.6cm) or abnormal (< 1.6cm)

3. To evaluate the change from baseline to 3 and 6 month visits in Plasma 5-hydroxyindoleacetic Acid (5-HIAA) levels in each arm. 5-HIAA is a standard test used in clinical practice to assess neuroendocrine tumor (NET) activity.
4. To evaluate the change from baseline to 3 and 6 month visits in high sensitivity troponin T in each arm
5. To evaluate the change from baseline to 3 and 6 month visits in health related quality of life with using the MD Anderson Symptom Inventory (MDASI) in each arm
6. To evaluate compliance of medications

Primary endpoint: The percent change in NT-proBNP at 6 month visit from baseline

Secondary Endpoints:

1. The change in 6MWT from baseline at 3 and 6 months
2. The change in CVHD score from baseline at 3 and 6 months , change (significant change or non-significant change) in global longitudinal myocardial strain assessment of the left and right ventricle from baseline at 3 and 6 months, change (normal or abnormal) in TAPSE from baseline at 3 and 6 months
3. The change in plasma 5-HIAA levels from baseline at 3 and 6 months
4. The change in high sensitivity troponin T from baseline at 3 and 6 months
5. The change in quality of life questionnaire (using MD Anderson Symptom Inventory (MDASI)) from baseline at 3 and 6 months
6. The proportion of patients maintaining at least 70% compliance

3.0 Background

3.1 Purpose

The basic hypothesis of our therapeutic programs in patients with carcinoid syndrome and carcinoid heart disease is to achieve meaningful and lasting symptom-improvement and look for responses to therapies that are associate with improved survival and favorable prognosis.

3.2 Historical Experience

Our group has a keen interest in the prevention, detection, and treatment of patients with carcinoid syndrome and those who develop carcinoid heart disease. Being part of MD Anderson Cancer Center, we have the unique advantage of having a robust GI medical oncology group and cardiology group that interact together and care for a significant number of patients with carcinoid syndrome and carcinoid heart disease. Most of these patients are treated with somatostatin analogs (SSA) therapy, but a significant portion have uncontrolled symptoms or develop carcinoid heart disease where medical therapy is limited and morbidity and mortality is extremely high.

3.3 Carcinoid Syndrome leading to Carcinoid Heart Disease: The role of Serotonin

Carcinoid tumors are rare neuroendocrine tumors (NETs) that can arise from enterochromaffin cells throughout the body. Some NETs are malignant and arise most commonly in the lung, rectum, and ileum (1). These malignant NETs metastasize to produce carcinoid syndrome. Patients with carcinoid syndrome present with vasomotor changes, diarrhea, hypotension, bronchospasm, and with carcinoid heart disease.
A large portion of patients with carcinoid syndrome are thought to develop carcinoid heart disease. In fact, carcinoid heart disease is the initial presentation of carcinoid syndrome in up to 20% of patients and occurs in more than 50% percent of these patients (2, 3).

Carcinoid heart disease is a result of plaque-like deposits of fibrous tissue composed of smooth muscle cells, myofibroblasts, extracellular matrix, and an overlying endothelial layer. These fibrous deposits affect cardiac valves. This leads to stenosis and/or regurgitation of the valve, with regurgitation being more common. Patients with carcinoid heart disease present with symptoms in the fifth to seventh decades of life (13-15). Because the clinical manifestations of this disease are subtle early in its course, diagnosis of carcinoid heart disease requires a high suspicion. In fact, in one study 37% of patients had no clinical signs of cardiac abnormalities by physical exam and 27% of patients with moderate to severe tricuspid regurgitation were in New York Heart Association class 1 (13). There is also a significant time lag from onset of symptoms to the diagnosis of this disease, ranging from 2 to 5 years before diagnosis is confirmed. Patients usually present with fatigue and dyspnea. In those with disease progression, right-sided heart failure occurs with edema, ascites, and dyspnea (16-18)

It is believed that alterations in the metabolism of serotonin, its associated receptors, and a transporter gene are involved in the mechanisms of serotonin-induced carcinoid heart disease (4, 5). Furthermore, indirect evidence of higher serotonin levels in patients with known carcinoid heart disease than in patients without carcinoid heart disease points to a role for high serotonin levels as a likely contributor to the development of carcinoid heart disease (6-8). More recently, researchers have implicated roles for serotonin and 5-hydroxytryptamine receptors in the development of valve disease. The activation of 5-hydroxytryptamine 2B receptors via expression of the tyrosine kinase SRC and mediation by transforming growth factor B1 promotes myofibroblast deposition and infiltration and activation of valvular interstitial cells, leading to fibrosis of the valves (5, 9-12).

3.4 Biomarkers in Carcinoid Heart Disease and Carcinoid Syndrome

While clinical signs maybe difficult to assess the role of the cardiac biomarkers has been studied and utilized in both patient with carcinoid heart disease and carcinoid syndrome. Patients with normal NT-proBNP levels have a better survival when they have carcinoid syndrome irrespective of whether or not they have carcinoid heart disease (17). Furthermore, NT-pro-BNP and 5-HIAA levels are independently associated with

symptom status and mortality in patients with metastatic NETs and carcinoid heart disease (26).

Patients with carcinoid heart disease in general have elevated NT-proBNP levels (Median 1,149 pg/ml vs 101 pg/ml) (18) highlighting the prognostic implications of this cardiac biomarker. Lastly, an NT-proBNP level cutoff of 260 pg/ml provides a high sensitivity (92%) and specificity (91%) to detect carcinoid heart disease (18). In fact this NT-ProBNP levels cutoff is being advocated in the Carcinoid Heart Disease expert statement for the screening and investigation of carcinoid heart disease (19).

As serotonin levels are implicated in both carcinoid syndrome and carcinoid heart disease, urinary 5-HIAA levels are also associated with the disease. In fact, a Urinary 5-HIAA level of >300 µmol/24 hours is associated with a 2.74-fold increase of the development and progression of carcinoid heart disease (20).

Furthermore, a novel echocardiographic technique, myocardial strain analysis, has some promising applications in patients with carcinoid disease. In a study using the RV free wall strain and tricuspid annular plane systolic excursion (TAPSE), it has been demonstrated that RV function is reduced in patients with intestinal carcinoid disease independent of obvious valvular involvement. This finding, in addition to the fact that patients with and without carcinoid heart disease showed slightly but significantly reduced LV global strain compared with healthy individuals, would suggest that that intestinal carcinoid disease may affect cardiac function before valvular involvement (25) and perhaps the possible role of serotonin in this process.

3.5 Cardiac Imaging in Carcinoid Disease and Carcinoid Heart Disease

Echocardiography has been the mainstay of evaluation of patients with carcinoid heart disease and is in fact recommend as a screening and investigational tool (19). Furthermore, a novel echocardiographic technique, known as myocardial strain analysis has some promising applications in patients with carcinoid disease. In a study using the RV free wall strain and tricuspid annular plane systolic excursion (TAPSE), it has been demonstrated that RV function is reduced in patients with intestinal carcinoid disease independent of obvious valvular involvement. This finding, in addition to the fact that patients with and without carcinoid heart disease showed slightly but significantly

reduced LV global strain compared with healthy individuals, would suggest that that intestinal carcinoid disease may affect cardiac function before valvular involvement (25) and perhaps the possible role of serotonin in this process.

3.6 Proposed Therapy with Telotristat Ethyl (XERMELO)

In this trial, we propose to use of telotristat ethyl in patients with carcinoid syndrome and carcinoid heart disease. We know that 5-HIAA and serotonin are implicated in both carcinoid syndrome and carcinoid heart disease. We know that telotristat ethyl works with SSA therapy to reduce hormone overproduction and control carcinoid syndrome diarrhea. We also know that the cardiac biomarker NT-proBNP provides prognostic information in these patients. In this study we propose that by using telotristat ethyl in conjunction with a SSA versus SSA alone, that telotristat ethyl will have a positive effect on hormone production and will demonstrate biochemical response in patients with known carcinoid syndrome and/or carcinoid heart disease.

4.0 Background and Drug Information

4.1 Background

Telotristat etiprate is the United States Adopted Name (USAN) for the hippurate salt of telotristat ethyl, the ethyl ester prodrug of LP-778902. In vivo, telotristat etiprate dissociates to form telotristat ethyl which is rapidly converted through the activity of carboxylesterase 1and 2 to its active metabolite LP-778902. Telotristat ethyl (XERMELO) is a novel, oral, small-molecule tryptophan hydroxylase (TPH) inhibitor that has a high molecular weight and acidic moieties, which inhibits it from crossing the blood-brain barrier. Telotristat ethyl has been shown to lower serotonin (5-HT) levels system by inhibiting TPH. Through inhibition of TPH, Telotristat ethyl reduces the production of peripheral 5-HT and the frequency of CS diarrhea and has been FDA approved for the treatment of carcinoid syndrome diarrhea. Two studies in patients with carcinoid syndrome suggested that telotristat etiprate, the hippurate salt of telotristat ethyl, reduced bowel movement (BM) frequency and decreased urinary 5-HIAA without overt CNS adverse effects (27,28). Although the name “telotristat etiprate” was previously granted by the United States Adopted Names Council and has been used in the literature, recent guidance from the US Food and Drug Administration recommends using the name of the neutral form (telotristat ethyl) rather than the name of the salt for drug products.

4.2 Preclinical Pharmacology Studies

Please refer to TerSera Therapeutics investigative brochure (IB) for details. Information in this proposal was derived from IB.

4.3 Preclinical Toxicology Studies

Please refer to TerSera Therapeutics investigative brochure (IB) for details.

4.4 Clinical Studies of telotristat ethyl in Humans

Please refer to TerSera Therapeutics investigative brochure (IB) for details

4.5 Rationale for telotristat ethyl (XERMELO) in patients with Carcinoid

Telotristat ethyl is indicated for the treatment of diarrhea in combination with SSA therapy in adults with inadequately controlled diarrhea on SSA therapy. This is thought to occur through the mediation of 5-HT. 5-HT is also implicated in the development of many of the signs and symptoms of carcinoid syndrome and carcinoid heart disease. A treatment which could further reduce 5-HT production may prove to be of immense clinical benefit. By adding a TPH inhibitor that can lower serotonin levels, telotristat ethyl could be of clinical benefit. One way to assess the potential of this clinical benefit is to look at the effect of telotristat ethyl on biomarkers such as NT-proBNP which have been associated with worsening cardiac prognosis. Furthermore, echocardiographic parameters and functional capacity changes can be clinically assessed.

4.6 Drug Product

4.6.1 Identity

Telotristat ethyl 250 mg and 500-mg tablets are white to off-white, coated, and oval. Placebo pills will be identical in size, shape, and color.

4.6.2 Drug Product Supply

Tablets will be supplied by TerSera Therapeutics and will include TELOTRISTAT ETHYL 250 mg tablets.

PLACEBO MATCHING 250 mg tablets.

4.6.3 Storage

Telotristat ethyl should be stored at 25°C (77°F); excursions are permitted 15°C to 30°C (59°F to 86°F).

5.0 Patient Eligibility

5.1 Inclusions

5.1.1 Patients who are ≥18 years old will be eligible for the study.

5.1.2 Histopathologically-confirmed, metastatic neuroendocrine tumor and/or locally/regionally advanced neuroendocrine tumor

5.1.3 Documented history of carcinoid syndrome based on clinical parameters

5.1.4 Currently receiving stable-dose somatostatin analog (SSA) therapy defined as ≥2 months

5.1.4.1 dose of long-acting release (LAR) or depot SSA therapy and on at least:

5.1.4.1.1 Octreotide LAR at 30 mg every 4 weeks

5.1.4.1.2 Lanreotide Depot at 120 mg every 4 weeks

5.1.4.1.3 Patients who cannot tolerate SSA therapy at a level indicated above will be allowed to enter at their highest tolerated dose

5.1.5 Ability and willingness to provide written informed consent

5.1.6 Patients of childbearing potential must agree to use an adequate method of contraception during the study and for 30 days after the last dose of telotristat ethyl.

5.1.6.1 a. Childbearing potential is defined as those who have not undergone surgical sterilization (eg. documented hysterectomy, tubal ligation, or bilateral salpingo-oophorectomy) or those who are not considered postmenopausal (defined as 12 months of spontaneous amenorrhea).

5.1.6.2 b. Adequate methods of contraception, defined as having a failure rate of <1% per year, for patients or their partner include the following: condom with spermicidal gel, diaphragm with spermicidal gel, intrauterine device, surgical sterilization, vasectomy, oral contraceptive pill, depo-progesterone injections, progesterone implant (ie, Implanon®), patch (Ortho Evra®), NuvaRing®, and abstinence. If a patient is not sexually active but becomes active, he or his partner should use medically accepted forms of contraception.

5.1.7 ECOG 0-2

5.2 Exclusions

5.2.1 Prior telotirstat exposure in the last 3 months

5.2.2 History of active treatment for malignancy, other than neuroendocrine tumor (malignancies that in the opinion of the Investigator are considered cured, may participate)

5.2.3 Treatment with any tumor directed therapy, including interferon, chemotherapy, mechanistic target of rapamycin (mTOR) inhibitors <4 weeks prior to screening, or hepatic embolization, radiotherapy, peptide receptor radionuclide therapy, and/or tumor debulking <12 weeks prior to screening

5.2.4 History of short bowel syndrome or other known causes of diarrhea unrelated to carcinoid syndrome

5.2.5 Clinically significant (as per primary investigators judgement) cardiac arrhythmia, bradycardia, tachycardia that would compromise patient safety or the outcome of the study

5.2.6 estimated glomerular filtration rate eGFR < 30ml/min

5.2.7 Hepatic laboratory values of aspartate transaminase (AST) or alanine aminotransferase (ALT):

5.2.7.1 a. >5 x upper limit of normal (ULN) if patient has documented history of hepatic metastases; or

5.2.7.2 b. >2.5 x ULN if no liver metastases are present

5.2.8 Pregnant or lactating patients

5.2.9 Patients receiving everolimus due to poor response to SSA

5.2.10 Life expectancy < 6 months

5.2.11 Any other clinically significant laboratory abnormality that would compromise patient safety or the outcome of the study as per primary investigators judgement

5.2.12 Any clinically significant and/or uncontrolled cardiac-related abnormality that would compromise patient safety or the outcome of the study including as per primary investigators judgement, but not limited to:

5.2.12.1 Arrhythmia causing hemodynamic compromise

5.2.12.2 Symptomatic severe valvular disease

5.2.12.3 Symptomatic congestive heart failure classified by New York Heart Association (NYHA) Class IV

5.2.12.4 Evidence of ischemia on ECG with chest pain

5.2.12.5 Unstable angina pectoris

5.2.13 Current complaints of persistent constipation or history of chronic constipation, bowel obstruction or fecaloma within the past 6 months

5.2.14 Investigator assessment of known history and/or uncontrolled hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus (HIV)-1 or HIV-2

5.2.15 History of substance or alcohol abuse (Diagnostic and Statistical Manual of Mental Disorders 5th edition [DSM-V] Criteria for Substance-Related Disorders) within the past 2 years

5.2.16 History of galactose intolerance, deficiency of Lapp lactase, or glucose-galactose malabsorption

5.2.17 Receipt of any investigational agent or study treatment (other treatment nor approved by FDA for carcinoid syndrome or carcinoid heart disease) within the past 30 days

5.2.18 Existence of any surgical or medical condition that, in the judgment of the Investigator, might compromise patient safety or the outcome of the study

5.2.19 Presence of any clinically significant findings (relative to the patient population) during review of medical history or upon PE that, in the Investigator's opinion, would compromise patient safety or the outcome of the study (eg, psychiatric illness/social situations that would limit compliance with study requirements)

5.2.20 Unable or unwilling to communicate or cooperate with the Investigator for any reason

6.0 Treatment Plan

6.1 General

All patients should be registered with the Data Management Office Prometheus system.

6.2 Treatment Plan

Patients who present to the MD Anderson Cancer Center and have a confirmed diagnosis of carcinoid syndrome and/or carcinoid heart disease based on clinical, imaging, and/or expert physician diagnosis would be eligible for enrollment in the trial (see above for eligibility criteria). Patients will be referred directly from oncology clinic and/or by electronic medical record screening by the research team to determine eligibility. Patients would then be enrolled into one of 2 arms of the clinical trial in a stratified randomized, double-blinded fashion into a treatment arm (XERMELO + SSA) versus a placebo standard treatment arm (PLACEBO + SSA). A maximum of 79 participants will be recruited to participate in the study for 6 months.

6.2.1 Screening Criteria and Randomization plan

Written, Electronic, or Virtual informed consent will be obtained from all patients before beginning any study related screening procedures. The collection of adverse events will begin after patient has received his first dose of treatment. Participants will be allocated to one of two treatment arms by stratified block randomization method, considering age group (≤60 years vs. >60 years) and disease status (with vs. without Carcinoid heart disease) as stratifying factors using Clinical trial conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct).

6.2.2 Study Overview

Study Type: Prospective Clinical Trial

Enrollment: 79 participants

Allocation: Randomized 1: 1

Intervention Model Description: Participants were randomized to one of two treatment arms by stratified randomization method. Those who were randomized to treatment arm would

receive telotristat ethyl 500 mg po TID + SSA and those who were randomized to placebo arm would receive placebo + SSA

Blinding: Double (Participant and Investigators)

Primary Purpose: Treatment and disease progression

6.2.3 Treatment Arms

Treatment Arm: A

Experimental: 500 mg Telotristat Ethyl (2 tablets of 250 mg) TID with meals + SSA Patients who are currently on stable-dose somatostatin analog (SSA)

therapy (octreotide or lanreotide for 2 months) are randomized to receive one 500 mg telotristat ethyl tablet administered three times daily for 6 months in the treatment period.

Placebo/Standard Treatment Arm: B

Placebo: Placebo-matching telotristat ethyl tablet TID with meals + SSA Patients who are currently on stable-dose somatostatin analog (SSA) therapy (octreotide or lanreotide for 2 months) are randomized to receive one placebo-matching 500 mg telotristat ethyl tablet administered three times daily for 6 months in the treatment period

6.3 Dose of Modifications of telotristat ethyl

6.3.1 Definitions

6.3.1.1 Interruption: temporary stoppage of telotristat ethyl but then resuming the treatment(s) within 3 weeks

6.3.1.2 Discontinuation: premature withdrawal from telotristat ethyl defined as a dose interruption lasting for >3 weeks

6.3.2 Dose Adjustments for adverse events related to the study drug

Adverse Events will be graded as follows (NCI CTCAE version 5.0)

Grade 1 No change in dose
Grade 2 Hold until ≤Grade 1. Resume at same dose level.
Grade 3 Hold until ≤Grade 1. Resume at 1 dose level lower (250 mg tid).
Grade 4 Hold and contact the Primary Investigator

Dose can also be adjusted or discontinued per PI's discretion for patients' safety.

*Patients unable to tolerate 250 mg tid should be discontinued from telotristat ethyl. **Constipation and abdominal pain dose adjustment is different (see below)

6.3.3 Recommended management for the following AEs:

6.3.3.1 Nausea and/or vomiting: treatment with antiemetics

6.3.3.2 Diarrhea: treat underlying cause and/or with antidiarrheal

6.3.3.3 Gastrointestinal toxicity

6.3.3.3.1 Monitor concomitant medication usage

6.3.3.3.2 Constipation (Grade 1 and above): initiate treatment as clinically indicated; examples of therapies include: laxatives, enemas, suppositories, psyllium hydration, over-the-counter (OTC) agents

6.3.3.3.3 Abdominal pain (Grade 1 and above): initiate treatment as clinically indicated; examples of therapies) include: analgesics, anti-gas/bloating agents

6.3.3.3.4 Hold telotristat ethyl for Grade 2 constipation or abdominal pain until ≤Grade 1.

6.3.3.3.5 Discontinue telotristat ethyl for Grade 3 constipation or abdominal pain*(please not this is different than above table)

6.3.3.4 Suicidal ideation: discontinue telotristat ethyl

6.4 Treatment Compliance

Patients will be asked to bring their unused or unopened bottles of telotristat ethyl to each visit. Patients will be allowed to ship their unused and/or unopened bottles of telotristat ethyl back to PI at MDAnderson if traveling is impossible/restricted. At each visit study site personnel will count returned tablets and reconcile the counts against planned number of doses for that interval. All dosages prescribed and dispensed to the patient, dose modification(s), and missed dose(s), including planned dose interruptions during the study must be recorded. Site personnel are to clarify any discrepancy and record this information.

Patients must maintain at least 70% compliance at clinical visits (3 month interval including allowed window; see section 8 for details) in dosing to be deemed as compliant.

6.5 Missed Doses

In the event of a missed or vomited telotristat ethyl dose, patients will take their subsequent dose at the next scheduled time point, following the tid dosing regimen of approximately every 6 hours. A dose outside of a 3-hour window for telotristat ethyl should be considered missed. Missed or vomited doses will not be made up.

6.6 Duration of Therapy

The total duration of therapy with the study drug telotristat ethyl will be 6 months as part of the clinical trial assessment.

6.7 Prohibited and Restricted Therapies During and Prior to the Study

Treatment with any tumor directed therapy, including interferon, chemotherapy, mechanistic target of rapamycin (mTOR) inhibitors <4 weeks prior to screening, or hepatic embolization, radiotherapy, radiolabeled SSA, and/or tumor debulking <12 weeks prior to screening. Patients receiving everolimus due to poor response to SSA

7.0 Baseline Evaluation

7.1 Obtain Informed Consent (telemedicine technology and language assistant may be used). We will follow the Office of Clinical Research Standard Operating Procedure (SOP) for informed consent process. During this process, the iConsent feature within EPIC will be utilized. The consent process can be completed either in-person or remote.

7.2 Complete history and physical examination including vital signs, NYHA classification, and ECOG (telemedicine technology and language assistant may be used)

7.3 CBC with differential, Liver panel (to include AST, ALT, bilirubin, albumin), basic metabolic panel (Sodium, potassium, bicarbonate, chloride, BUN, creatinine, glucose) within 6 weeks (**-asterisk- labs and tests maybe done 3 weeks prior or up to 3 weeks after clinical baseline/follow-up date)

7.4 ECG within 6 weeks**

7.5 Serum Pregnancy test for females of childbearing age within 1 week

7.6 MD Anderson Symptom Inventory MDASI module (in Appendix) within 6 weeks (telemedicine technology and language assistant may be used)**

7.7 Echocardiography with a 2D transthoracic echocardiography (2D TTE), 3-dimensional echocardiography (3D TTE), and myocardial strain of the left and right ventricle within 6 weeks**

7.8 Plasma 5-HIAA collection within 6weeks** (it will be kept frozen in Cryogene lab and will be transferred to Frontage Lab for analysis. More information is included in the lab manual.)

7.9 Cardiac biomarkers to include: N-terminal pro B-type natriuretic peptide (NT-proBNP) and high sensitivity troponin T (HS-troponin T) within 6 weeks**

7.10 6 minute walk test (6MWT) (in Appendix) where distance is recorded in meters within 6 weeks**

7.11 Assessment for Depression: Validated 2 question case finding instrument: (1) “During the past month, have you often been bothered by feeling down,

depressed, or hopeless?" and (2) "During the past month, have you often been bothered by little interest or pleasure in doing things? (telemedicine technology and language assistant may be used)

** labs and tests maybe done 3 weeks prior or up to 3 weeks after clinical baseline/follow-up date (this is defined as acceptable time window)
Above labs and tests from other institutions can be used in lieu of labs done at clinical research site

8.0 Evaluation during Study

8.1 Complete history and physical examination done at 3 and 6 months as part of clinical follow-up. (telemedicine technology and language assistant may be used) **A window of 3 weeks before or after for these visits will be acceptable to accommodate for patient convenience.

8.2 CBC with differential, Liver panel (to include AST, ALT, bilirubin, albumin), basic metabolic panel (Sodium, potassium, bicarbonate, chloride, BUN, creatinine, glucose) done at 3 and 6 month (**-asterisk- labs and tests maybe done 3 weeks prior or up to 3 weeks after clinical follow-up date)

8.3 ECG done at 3 and 6 months within 6 weeks of clinical visit**

8.4 Pregnancy test for females of childbearing age within one week

8.5 MDASI done at 3 and 6 months (telemedicine technology and language assistant may be used;can be done within 6 weeks of clinical follow-up)

8.6 Echocardiography with a 2D transthoracic echocardiography (2D TTE), 3-dimensional echocardiography (3D TTE), and myocardial strain of the left and right ventricle to be done at 3 and 6 months for those patients with carcinoid heart disease and with carcinoid syndrome and high suspicion of carcinoid heart disease (CHD group), such as those with clinical features or increased NT-proBNP (> 260) mg/ml and/or 5-HIAA levels (24 hr urine 5-HIAA > 100 mg). (**-asterisk- labs and tests maybe done 3 weeks prior or up to 3 weeks after clinical follow-up date

8.7 Echocardiography will be done at 6 months in patients with carcinoid syndrome (CS group) who do not have high suspicion for carcinoid heart disease

8.8 Plasma 5-HIAA collection at 3 and 6 months (**-asterisk- labs and tests maybe done 3 weeks prior or up to 3 weeks after clinical follow-up date) (it will be kept frozen in Cryogene lab and will be transferred to Frontage Lab for analysis. More information is included in the lab manual.)

8.9 Cardiac biomarkers to include: N-terminal pro B-type natriuretic peptide (NT-proBNP) and high sensitivity troponin T (HS-troponin T) at 3 and 6 months (**-asterisk- labs and tests maybe done 3 weeks prior or up to 3 weeks after clinical baseline/follow-up date)

8.10 6 minute walk test (6MWT) where distance is recorded in meters at 3 and 6 months (**-asterisk- labs and tests maybe done 3 weeks prior or up to 3 weeks after clinical follow-up date)

8.11 Assessment for Depression at 3 and 6 month (**following window above) clinical follow-up: Validated 2 question case finding instrument: (1) “During the past month, have you often been bothered by feeling down, depressed, or hopeless?” and (2) “During the past month, have you often been bothered by little interest or pleasure in doing things? (telemedicine technology and language assistant may be used)

8.12 Data on hospitalization, death, routine clinical data, and routine imaging data (such as CT scan, MRI, PET, and echocardiography) will be collected and explored with correlation with study interventions

8.13 Study schedule (table)

	Baseline	3 Months**	6 Months**
Clinical /Virtual Clinic Follow-up	X	X	X
CBC with Diff Basic Metabolic Panel (BMP) LFTs	X	X	X
ECG	X	X	X

Pregnancy Test ^ (for females of childbearing age)	X	X	X
Echocardiography (CHD group)	X	X	X
Echocardiography (CS group)	X		X
Plasma collection for 5-HIAA	X	X	X
NT-proBNP	X	X	X
Hs-troponin T	X	X	X
6 minute walk test	X	X	X
MDASI	X	X	X
Depression Assessment	X	X	X

(**-asterisk- labs and tests maybe done 3 weeks prior or up to 3 weeks after clinical baseline/follow-up date. ^- pregnancy test will be within one week of visit)

8.14 Call schedule during study

Patients will be called by Research team once a week for the first month after baseline and monthly afterwards except for the months with clinical visit (3 month visit, 6 month visit) to assess for potential toxicities, adverse events, treatment compliance, and answer patient questions.

*Research Phone Calls have a time window of +/- 1 business day to account for institutional holidays and subject availability.

*Patients with adverse events noted on the call will be called every week until the adverse events resolve.

*If a dosage change is made after the first month the patient will be called the following week for assessment.

	Research Call	Clinical Visit
Week 0 (Baseline)		X
Week 1	X	

Week 2	X	
Week 3	X	
Week 4	X	
Week 8	X	
Week 12 (3 months)		X
Week 16	X	
Week 20	X	
Week 24 (6 months)		X

9.0 Criteria for response/change

9.1 Biochemical response/change.

9.1.1 5-HIAA levels- response will be defined as a reduction in plasma5-HIAA of 30%

9.1.2 Change in NT-ProBNP

9.1.3 Change in HS-troponin T

9.2 Echocardiographic response

9.2.1 Echocardiographic scoring system for CVHD- response will be defined as a change in CVHD score of 10%

9.2.2 Myocardia strain assessment- response will be defined as a change in global longitudinal strain by 15%

9.3 Functional response/change

9.3.1 Change in 6MWT by 50 meters would considered significant

10.0 Criteria for Removal from the Study

10.1 Patient request/consent withdrawal

10.2 Noncompliance, including failure to adhere to the study requirements as in the study protocol, and/or lost to follow-up

10.3 Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study

10.4 Pregnancy

10.5 Patient is unable to tolerate telotristat ethyl following dosage reduction to 250 mg tid

10.6 Patient experiences:

10.6.1 Unresolved Grade 3 constipation as graded by the NCI CTCAE v5.0;

10.6.2 Development of severe, persistent, or worsening abdominal pain

10.6.3 Grade 4 toxicity

10.6.4 Suicidal ideation

10.6.5 Death

11.0 Statistical Consideration

11.1 Sample Size Justification

Primary endpoint is the percent change in NT-proBNP at 6 months from baseline, which is defined as the absolute change divided by the baseline value multiplied by 100. A total sample size of 60 (30 in each group) will be enrolled, accounting for ~13% drop out rate to have 52 subjects with a primary endpoint. Enrolled participants who were dropped out of study will be replaced with additional participants if more than 13% participants were dropped out of the study. A sample size of 30 in each group produces a 95% confidence interval equal to the sample mean change in NT-proBNP plus or minus 10 when the estimated standard deviation is 25, accounting for ~13% drop out rate. There is no preliminary data and there are no similar studies to obtain preliminary estimates for the percent change in NT-proBNP in any of 2 arms.
Therefore, the sample size calculation was performed based on an effect size of 0.8, which is considered as large. Group sample sizes of 30 and 30 achieve 80% power to detect a standard effect size of 0.8 (for example, mean percent difference of 20 when the standard deviation of 25) with a significance level (alpha) of 0.05 using a two-sided two-sample t-test, accounting for ~13% drop out rate. PASS 2005 (Hintze, J. (2004). NCSS and PASS. Number Cruncher Statistical Systems. Kaysville, Utah. www.ncss.com) was used for the sample size calculation. The caveat is that if the true effect size is smaller than the effect used in power calculation then the calculated sample size will not be enough to achieve 80% power. In case the study turns to be not significant but promising in this setting, these data can be used as preliminary estimates to design a bigger trial.

After enrolling 60 subjects, we evaluated the observed drop-out rate. Three subjects were not randomized yet. Six-month follow-up was not reached for 13 subjects. Sixteen subjects were dropped out of the study (withdrawn prior to randomization (n=6), randomized but withdrawn prior to receiving study treatment (n=4), and randomized, treated, but withdrawn prior to 6-month follow-up (n=6)). Drop-out rate among those who were enrolled, excluding those not reaching 6-month follow-up and those not randomized yet, is 36% (16/44). Since the drop-out rate is higher than 13%, we will enroll additional subjects to replace those who dropped out of the study.

Among those who received the study drug, 28 subjects have completed 6-month follow-up; 13 subjects were not reached 6-month follow-up yet; 6 subjects were withdrawn prior to 6-month follow-up. 6-month follow-up completion rate among those who received the study drug and reached 6-month follow-up visit is 82% (28/34). At this rate, we expect that 10 of 13 not reaching 6-month will complete 6-month follow-up. To have 52 subjects with a primary endpoint, we still need 14 (i.e., 52-38) additional subjects with a primary endpoint.

Applying the drop-out rate of 36%, we may need to enroll 19 additional subjects in addition to 3 subjects who were not randomized yet. As we enroll additional subjects in the study, we will monitor the number of subjects who complete 6-month follow-up with a primary endpoint. Our goal is to have 52 subjects with a primary endpoint. We will stop enrolling additional subjects once the number of subjects who complete 6-month follow-up with a primary endpoint reaches 52.

If needed, we will evaluate the observed drop-out rate and re-estimate the number of

additional subjects to enroll to have 52 subjects with a primary endpoint after enrolling 19 additional subjects,

11.2 Statistical Analysis Plan

We will analyze two analysis sets, including modified intention-to-treat and per protocol analysis sets. Modified intention-to-treat analysis set will include all patients who were randomized and started a study treatment, regardless of whether they received treatment as planned. Per protocol analysis set will include all patients who received treatment as planned.

Patient baseline characteristics and outcome variables (primary endpoint and secondary endpoints (absolute changes and percent changes for continuous endpoints)) will be summarized by study arm, using mean (standard deviation (SD)) or median (inter quartile range (IQR)) for continuous variables and frequency (%) for categorical variables. Repeatedly measured variables will be summarized using descriptive statistics by study arm and by time point (baseline, 3 months, and 6 months). The mean percent

change in NT-proBNP at 6 months from baseline will be estimated in each arm along with the standard deviation. The mean percent change in NT-proBNP will be compared between 2 arms by two-sample t-test. Linear regression model will be used to compare the 2 arms in the mean percent change, adjusting for stratification factors. Those without 3-months or 6-months NT-proBNP may be imputed, using last observation carried forward method or other methods.

Compliance is defined as the total number of medications taken divided by the total number of medications provided during 6 month treatment period. The proportion of patients maintaining at least 70% compliance will be estimated in each arm. Proportion of patients experiencing each type of side effects will be estimated in each arm along with 95% confidence interval (CI). The change from baseline to 3 months and the change from baseline to 6 months in variables described in secondary objectives will be compared within each arm by paired t-test or Wilcoxon signed-rank test for continuous variables and Mantel-Haenszel test for categorical variables. Generalized linear mixed effects models will be used to compare two arms in repeatedly measured outcomes over time. P-values less than 0.05 will indicate statistical significances. SAS 9.4 (Cary, NC) and other relevant software will be used for statistical analysis.

11.3 Toxicity Monitoring

Telotristat is an FDA approved drug for management of diarrhea in patients with carcinoid syndrome in patients who are on SSAs. The FDA approved dose is 250 mg to be taken by mouth with meals three times daily. In this study we will also be using telotristat in patients with carcinoid syndrome but with a dose of 500mg three times daily. Both dosing regimens (250mg TID and 500 mg TID) were used in the phase 3 TELESTAR trial along with a companion phase 3 trial, TELECAST, which assessed the safety and efficacy of telotristat ethyl in patients with carcinoid syndrome during a 12-week double-blind treatment period followed by a 36-week open-label extension (OLE). The overall incidence of treatment related adverse events was similar among all groups. During a 12 week period, 5 patients (19.2%) in the placebo group experienced a serious adverse event (SAE), whereas only 1 patient (4.0%) and 3 patients (12.0%) experienced a SAE in the telotristat ethyl 250 mg and telotristat ethyl 500 mg groups.

Given the safety and efficacy of this FDA approved drug has been established we will not be conducting toxicity monitoring (Pavel et al. doi: 10.1530/ERC-17-0455).

12.0 Reporting Requirements

Data and safety monitoring will be conducted by MD Anderson Cancer Center DSMB.

12.1 Adverse Event Reporting

These guidelines serve to bring the Department of Cardiology in compliance with the institutional policy on Reporting of Serious Adverse Events-definition of expected AE-" All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study treatment" and Guideline for Good Clinical Practice 4.11.1

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the first protocol intervention, even if the event is not considered to be related to study treatment. Medical conditions/diseases present before starting study therapy are only considered adverse events if they worsen after starting study treatment. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

For each AE, the Investigator will assess the causal relationship between each of the study drugs and the AE using their clinical expertise and judgment according to the most appropriate description as follows:

• **Not related**: The AE does not follow a reasonable temporal relationship to administration of the study drug, or an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is more likely
• **Unlikely related:** The AE has an improbable temporal relationship to administration of the study drug, or an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is more likely
• **Possibly related**: The AE follows a reasonable temporal relationship to administration of the study drug (including the course after withdrawal of the drug), and an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is equally or less likely
• **Probably related**: The AE follows a reasonable temporal relationship to administration of the study drug (including the course after withdrawal of the drug), and an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is unlikely
• **Definitely related**: The AE follows a plausible temporal relationship to administration of the study drug (including the course after withdrawal of the drug) and alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) can be ruled out. Positive rechallenge (ie, reappearance or worsening of the AE after study drug is reintroduced) or a response pattern known to be associated with administration of the study drug provides further evidence of a definitive causality assessment.

Adverse Events (AEs) will be evaluated according to CTC version 5 in each protocol. AEs will be documented in an AE log. Prometheus will be used to enter data for this protocol. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Severity of the adverse events (AEs) -The severity of the adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V.05. Events not included in the NCI CTCAE will be scored as follows:
General grading:
• Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.

- Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
- Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- Grade 4: Life Threatening: discomfort that represents immediate risk of death

Recommended Adverse Event Recording Guidelines

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

Expected events during carcinoid syndrome and carcinoid heart disease therapy are:

a. Nausea
b. Headache
c. Edema
d. Flatulence
e. Pyrexia
f. Decreased appetite
g. Fatigue
h. Flushing
i. Diarrhea
j. Constipation
k. Abdominal pain
l. electrolyte abnormalities (sodium, potassium, CO2, magnesium)

m. chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)
n. coagulation abnormalities
o. bone, joint, or muscle pain
p. liver function test abnormalities associated with infection or disease progression
q. disease progression
r. volume overload
s. signs and symptoms of heart failure
t. arrhythmias such as atrial fibrillation, atrial flutter, and supraventricular tachycardia
u. development of depression - **patients with depression and suicidal ideation will be referred immediately to psychiatry services as per institutional guidelines **

12.2 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse (possible, probable, and definite AE) reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events”. Unless stated otherwise in the protocol, all prompt SAEs, unexpected and related, must be reported to the IRB (within 10 working days of knowledge of the event).
- The MDACC “Internal SAE Report Form for Prompt Reporting” will be used for reporting
. • Elective admissions or admissions for transfusions will not be considered an SAE.
- Serious adverse events will be captured from the time the patient take his first treatment drug dose until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that are reported to the treatment team that occur after the 30 day time period that are related to the study treatment must be reported to the IRB. This may include the development of a secondary malignancy.

- Primary investigator and research team may become unblinded to the study arms if it is deemed a medical necessity required for patient treatment or safety.

Reporting to FDA:

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

12.3 Investigator Communication with Supporting Company

All SAEs, regardless of causal relationship to study drug, and pregnancies must be reported to the TerSera Therapeutics within 72 hours of investigational site awareness of the event. Investigators should not wait for complete information on an event before notifying the TerSera Therapeutics of an SAE.
Investigational site personnel must use the approved method of notification per the TerSera Therapeutics to report these events.
If paper report forms are used, the form(s) should be sent to:
Safety Data Facsimile: (832) 442-5462 or
Email address (in case of fax failure): Medicalinformation@tersera.com
In case of failure of/lack of access to eCRF, email, or fax, the event should be reported to the TerSera Medical Information Call Center within one business day of awareness: (844) 334-4035
If an SAE is reported via telephone, the telephone report should be followed by a written report using a reporting method described above (ie, completion of eCRF of paper form).

12.4 Reporting of External SAEs

The MDACC institutional policy for reporting of external SAEs will be followed.

12.5 Follow-up of Adverse Events

All AEs should be followed until the event has resolved, the condition has stabilized, the patient is lost to follow-up, or at least 30 days following the last dose of any study drug. Final known outcome must be reported whenever possible. Medically significant abnormal laboratory test results should be

repeated and followed until the test results have returned to the normal range or Baseline value, and/or an adequate explanation of the abnormality is determined

13.0 Appendix

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

MD Anderson Symptom Inventory - Heart Failure (MDASI-HF)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with lack of energy at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

Heart Failure (HF)

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your problem with **abdominal bloating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your problem with **ankle swelling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **sleeping without adding more pillows under your head** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your problem with **lack of energy** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your problem with **racing heartbeat (palpitation)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your problem with **nighttime cough** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your problem with **waking up at night with difficulty breathing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your problem with **sudden weight gain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms inter… …ur li…

Symptoms frequently interfere with how … …el… …ction. How much have your symptoms interfered with the following items *in the last 24 hours*? Ple… selec… …ber from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	…not …fere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
22. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
23. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
24. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
25. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
26. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
27. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

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*****Please note below information will be entered electronically using the tablet*****

TIME _____

Date:_____ MRN: _____

Patient Name:_____ Sex: **M** / **F**

Ord. Physician:_____Ord. #_____

Resting	
Heart Rate	
Oxygen saturation	
Borg Scale Dyspnea	
Borg Scale Fatigue	
Blood Pressure Systolic	
Blood Pressure Diastolic	
Supplemental Oxygen	
During Test	
Highest Heart Rate	
Lowest Oxygen Saturation	
Borg Scale Dyspnea	
Borg Scale Fatigue	
Blood Pressure Systolic	
Blood Pressure Diastolic	
Number of Pauses	
Duration of Test	
Six Minute Walk Distance	
Post Test	
Oxygen Saturation Post Test	
LAPS	

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