GI 221

A Phase II Study of Lanreotide in Patients with Metastatic Gastrointestinal Neuroendocrine Tumors Undergoing Liver-directed Radioembolization with Yttrium-90 Microspheres (SIR-Spheres®)

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY NUMBER:	GI 221
STUDY DRUG:	Lanreotide
SPONSOR:	Sarah Cannon Development Innovations, LLC (Sarah Cannon Innovations) 1100 Charlotte Avenue, Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	Johanna Bendell, MD Sarah Cannon 1100 Charlotte Avenue, Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI
DATE FINAL:	28 April 2016
AMENDMENT 1:	24 February 2017

SARAH CANNON
Development Innovations

Clinical Study Statement of Compliance

A Phase II Study of Lanreotide in Patients with Metastatic Gastrointestinal Neuroendocrine Tumors Undergoing Liver-directed Radioembolization with Yttrium-90 Microspheres (SIR-Spheres®)

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

SARAH CANNON
Development Innovations

Clinical Study Signature Approval Page

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Study Chair **Sarah Cannon**	**Study Chair Signature**	**Date**
Sponsor Representative **Sarah Cannon Development Innovations, LLC**	**Sarah Cannon Development Innovations, LLC Representative Signature**	**Date**

SARAH CANNON
Development Innovations

Clinical Study Principal Investigator Signature Form

A Phase II Study of Lanreotide in Patients with Metastatic Gastrointestinal Neuroendocrine Tumors Undergoing Liver-directed Radioembolization with Yttrium-90 Microspheres (SIR-Spheres®)

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DATE FINAL:	28 April 2016
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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
ATTN: Regulatory Department
1100 Charlotte Avenue, Suite 800
Nashville, TN 37203

SARAH CANNON
Development Innovations

GI 221 Summary of Change

AMENDMENT NUMBER: 1 **AMENDMENT DATE:** 24 February 2017

Global Changes

The name Sarah Cannon Research Institute (SCRI) Development Innovations, LLC, has been changed throughout to Sarah Cannon Development Innovations, LLC, and the former logo has been replaced with the new company logo. A few minor typographical errors have been corrected.

Protocol Synopsis and Section 3.1 – Inclusion Criteria

8. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for ~~30 days~~ ***3 months (90 days)*** following last dose of study drug(s). Male patients must also refrain from donating sperm during their participation in the study ***and for 3 months (90 days) after the last dose of study drug*** (Appendix C).

Protocol Synopsis and Section 3.2 – Exclusion Criteria

12. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C. ***Laboratory test results ≤ 1 year will be confirmed by the treating physician prior to study enrollment. If results are ≥ 1 year old, a fresh blood sample will be required for a new test.***

Section 7.1 – Study Assessments and Evaluations - Overview

The baseline physical examination, medical history, ECOG PS, electrocardiogram (ECG), complete blood counts (CBC), 3-part differential and platelets, comprehensive metabolic profile (CMP)~~, urinalysis,~~ and prothrombin time (PT)/partial thromboplastin time (PTT)/International Normalization Ratio (INR) should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. CT scans should be performed ≤28 days prior to initiation of treatment.

Section 7.2 – Baseline Study Assessments and Appendix D

- ***Results of HIV, hepatitis B, and hepatitis C tests will be confirmed if taken within the past 1 year. If test results are >1 year old, patient will be required to provide a fresh blood sample for a new test.***

The ICF associated with this protocol is being updated accordingly.

GI 221 PROTOCOL SYNOPSIS

Title of Study:	A Phase II Study of Lanreotide in Patients with Metastatic Gastrointestinal Neuroendocrine Tumors Undergoing Liver-directed Radioembolization with Yttrium-90 Microspheres (SIR-Spheres®)
Sarah Cannon Innovations Study Number:	GI 221
Sponsor:	Sarah Cannon Development Innovations, LLC – Nashville - TN
Study Duration:	The total duration of the study is planned to be 3 years. **Phase of Study:** II
Study Centers:	This study will be conducted at approximately 5 sites in the Sarah Cannon network in the United States.
Number of Patients:	Up to 25 patients are planned to be enrolled in this study.
Objectives:	**Primary Objective** The primary objective of this study is to: • Evaluate the safety of concomitant administration of lanreotide for patients undergoing liver-directed radioembolization with yttrium-90 microspheres (SIR-Spheres). **Secondary Objectives** The secondary objective of this study is to: • Evaluate the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
Study Design:	This is an open-label, prospective, multi-center Phase II study for patients with metastatic well-to-moderately differentiated neuroendocrine tumors (including typical carcinoid and pancreatic neuroendocrine tumors) who are candidates for liver-directed radioembolization. Patients will receive treatment with lanreotide (120 mg subcutaneously (SQ) every 28 days) in combination with SIR-Spheres treatment (dose and treatment day to be determined by treating radiation oncologist).
Study Drugs, Doses, and Modes of Administration:	Lanreotide 120 mg Day 1 of every cycle (every 28 days) by deep subcutaneous injection. SIR-Spheres TBD

GI 221 PROTOCOL SYNOPSIS

Inclusion Criteria:	1. Metastatic well-to-moderately differentiated (or low-grade) neuroendocrine carcinoma, including typical carcinoid or pancreatic islet cell carcinoma. 2. Computerized tomography (CT) scan evidence of liver metastases which are not treatable by surgical resection or local ablation with curative intent at the time of study entry. If a CT scan is not possible, then an MRI may be used. 3. Patients who are currently receiving or have previously received lanreotide or another somatostatin analogue are eligible. Previous treatment with lanreotide or another somatostatin analogue is not required for study entry. 4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A). 5. Adequate hematologic function defined as: • Absolute neutrophil count (ANC) ≥1500/μL • Hemoglobin (Hgb) ≥9 g/dL • Platelets ≥100,000/μL 6. Adequate liver function defined as: • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) • Total bilirubin ≤1.2 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin) 7. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L) OR calculated creatinine clearance ≥50 mL/min as calculated by Cockcroft and Gault Formula. 8. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 3 months (90 days) following last dose of study drug(s). Male patients must also refrain from donating sperm during their participation in the study and for 3 months (90 days) after the last dose of study drug (Appendix C). 9. Life expectancy ≥ 3 months. 10. Age ≥18 years. 11. Willingness and ability to comply with study and follow-up procedures. 12. Ability to understand the nature of this study and give written informed consent.

Exclusion Criteria:	1. Anti-cancer therapy with the exception of lanreotide or another somatostatin analogue within 21 days or 5 half-lives (whichever is shorter) of starting study treatment. 2. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to Cycle 1 Day 1 or has not recovered from side effects of such therapy. 3. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement. 4. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy. 5. Clinically significant ascites, cirrhosis, portal hypertension, or thrombosis as determined by clinical or radiologic assessment. 6. Pregnant or lactating 7. Acute or chronic liver, renal, or pancreas disease. 8. Any of the following cardiac diseases currently or within the last 6 months: − Left Ventricular Ejection Fraction (LVEF) <45% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO) − QTc interval >480 ms on screening electrocardiogram (ECG) − Unstable angina pectoris − Congestive heart failure (New York Heart Association (NYHA) ≥ Grade 2 [Appendix B]) − Acute myocardial infarction − Conduction abnormality not controlled with pacemaker or medication − Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible) − Valvular disease with significant compromise in cardiac function 9. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure (DBP) >100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment). 10. Currently receiving treatment with therapeutic doses of warfarin sodium. Low molecular weight heparin is allowed. 11. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. 12. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C. Laboratory test results ≤1 year will be confirmed by the treating physician prior to study enrollment. If results are ≥1 year old, a fresh blood sample will be required for a new test. 13. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer. 14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

Statistical Methodology:	This study will test no formal hypothesis. The sample size of 25 patients is based on clinical practicalities rather than statistical reasoning, in order to evaluate the safety of administration of lanreotide and SIR-Spheres.

GI 221 CONTACT INFORMATION

Sarah Cannon Innovations **Contact Information:**	Sarah Cannon Development Innovations 1100 Charlotte Avenue, Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
Study Chair:	Johanna Bendell, MD Sarah Cannon 1100 Charlotte Avenue, Suite 800 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
Safety Dept. Fax #: **Safety Dept. Email:**	1-866-807-4325 CANN.SAE@SCRI-Innovations.com
Regulatory Phone # **Regulatory Email:**	1-877-MY-1-SCRI SCRIRegulatory@SCRI-Innovations.com
Sarah Cannon Innovations Enrollment Phone #: **Sarah Cannon Innovations Enrollment Fax #:** **Sarah Cannon Innovations Enrollment Email:**	1-877-MY-1-SCRI 1-866-346-1062 or 615-524-4012 CANN.SCRIInnovationsENR@scri-innovations.com

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST (SGOT)	Aspartate aminotransferase
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete response/remission
CRF	Case Report Form
CT	Computerized tomography
DCR	Disease control rate
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PHI	Protected health information
PFS	Progression-free survival
PR	Partial response/remission
QA	Quality assurance
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event

LIST OF ABBREVIATIONS (continued)

SAR	Suspected adverse reaction
Sarah Cannon Innovations	Sarah Cannon Development Innovations, LLC
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reaction
UAE	Unexpected Adverse Event
ULN	Upper limit of normal

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1. INTRODUCTION

It is estimated that 8,000 people are diagnosed with neuroendocrine tumors (NETs) and cancers originating in the gastrointestinal tract (the stomach, intestine, appendix, colon, or rectum) each year in the United States (US). The US Food and Drug Administration (FDA) has approved lanreotide (Somatuline® Depot Injection, Ipsen Pharma) to treat advanced gastrointestinal neuroendocrine tumors and advanced pancreatic neuroendocrine tumors.

1.1 Background

For patients with unresectable liver metastases from NETs, radioembolization (RE) can achieve durable hepatic tumor response while alleviating symptoms. Radioembolization with yttrium-90 microspheres (SIR-Spheres® therapy) is FDA approved for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of floxuridine (FUDR). SIR-Spheres therapy enables multiple liver metastases to be targeted in a single procedure, and delivers targeted radiation to these tumors while limiting the dose experienced by normal liver parenchyma (Kennedy et al 2012(a), Kennedy et al 2012(b)).

An objective response rate (ORR) of 63% was reported in a retrospective review of 148 patients with unresectable liver metastases from NETs who received SIR-Spheres therapy; two-thirds of patients did not experience acute or delayed grade 3/4 toxicity (Kennedy et al 2008). A prospective Phase II trial was conducted, in which SIR-Spheres were administered in combination with a 7-day infusion of 5-fluorouracil to 34 patients with unresectable metastatic NETs (mNETs) (King et al 2008). A radiographic response by Response Evaluation Criteria in Solid Tumors (RECIST) was reported in 50% of these patients.

In NETs that express somatostatin receptors, somatostatin analogues can control hypersecretion and help manage symptoms. In addition, some of these agents have recently been shown in controlled trials to have some anti-proliferative effects. Lanreotide is a somatostatin analogue which was shown to significantly prolong progression-free survival (PFS) in patients with gastroenteropancreatic NETs compared to placebo in the CLARINET trial (Caplin et al. 2014).

1.2 Rationale for the Study

To our knowledge, there have not been studies conducted to formally assess the safety of co-administration of lanreotide and RE with SIR-Spheres. However, given the promising results of each of these individual treatments in this patient population, it is important to determine how to optimize these therapies for patients with NETs.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

- Evaluate the safety of concomitant administration of lanreotide for patients undergoing liver-directed radioembolization with yttrium-90 microspheres (SIR-Spheres).

2.2 Secondary Objectives

The secondary objective of this study is to:

- Evaluate the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in the research study:

1. Metastatic well-to-moderately differentiated (or low-grade) neuroendocrine carcinoma, including typical carcinoid or pancreatic islet cell carcinoma.
2. Computerized tomography (CT) scan evidence of liver metastases which are not treatable by surgical resection or local ablation with curative intent at the time of study entry. If a CT scan is not possible, then an MRI may be used.
3. Patients who are currently receiving or have previously received lanreotide or another somatostatin analogue are eligible. Previous treatment with lanreotide or another somatostatin analogue is not required for study entry.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A).
5. Adequate hematologic function defined as:
   - Absolute neutrophil count (ANC) ≥1500/μL
   - Hemoglobin (Hgb) ≥9 g/dL
   - Platelets ≥100,000/μL
6. Adequate liver function defined as:
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN)
   - Total bilirubin ≤1.2 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
7. Adequate renal function defined as serum creatinine ≤1.5 mg/dL (133 μmol/L) OR calculated creatinine clearance ≥50 mL/min as calculated by Cockcroft and Gault Formula.
8. Male patients with female partners of childbearing potential and women patients of childbearing potential are required to use two forms of **acceptable** contraception,

including one barrier method, during their participation in the study and for 3 months (90 days) following last dose of study drug(s). Male patients must also refrain from donating sperm during their participation in the study and for 3 months (90 days) after the last dose of study drug (Appendix C).

9. Life expectancy ≥ 3 months.
10. Age ≥18 years.
11. Willingness and ability to comply with study and follow-up procedures.
12. Ability to understand the nature of this study and give written informed consent.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Anti-cancer therapy with the exception of lanreotide or another somatostatin analogue within 21 days or 5 half-lives (whichever is shorter) of starting study treatment.
2. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to Cycle 1 Day 1 or has not recovered from side effects of such therapy.
3. Major surgical procedures ≤28 days of beginning study drug, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement.
4. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if therapy was completed at least 2 weeks prior to study entry and there is no evidence of central nervous system disease progression, mild neurologic symptoms, and no requirement for chronic corticosteroid therapy.
5. Clinically significant ascites, cirrhosis, portal hypertension, or thrombosis as determined by clinical or radiologic assessment.
6. Pregnant or lactating
7. Acute or chronic liver, renal, or pancreas disease.
8. Any of the following cardiac diseases currently or within the last 6 months:
    - Left Ventricular Ejection Fraction (LVEF) <45% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc interval >480 ms on screening electrocardiogram (ECG)
    - Unstable angina pectoris
    - Congestive heart failure (New York Heart Association (NYHA) ≥ Grade 2 [Appendix B])
    - Acute myocardial infarction
    - Conduction abnormality not controlled with pacemaker or medication

- Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
- Valvular disease with significant compromise in cardiac function

9. Inadequately controlled hypertension (i.e., systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure (DBP) >100 mmHg) (patients with values above these levels must have their blood pressure (BP) controlled with medication prior to starting treatment).
10. Currently receiving treatment with therapeutic doses of warfarin sodium. Low molecular weight heparin is allowed.
11. Serious active infection at the time of treatment, or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.
12. Known diagnosis of human immunodeficiency virus, hepatitis B, or hepatitis C. Laboratory test results ≤1 year will be confirmed by the treating physician prior to study enrollment. If results are ≥1 year old, a fresh blood sample will be required for a new test.
13. Presence of other active cancers, or history of treatment for invasive cancer ≤5 years. Patients with Stage I cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.
14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Non-compliance/lost to follow-up
- Pregnancy

After discontinuation from protocol treatment, patients must be followed for adverse events (AEs) for 30 calendar days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve, because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment in the eCRF.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, side-effects, risks, and discomforts. Institutional Review Board (IRB) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through Sarah Cannon Development Innovations (Sarah Cannon Innovations). Registration may be made via email CANN.SCRIInnovationsEnr@scri-innovations.com or fax 866-346-1062, Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time. Patient registration will be confirmed via email within 24 hours, or by the next business day.

5. STUDY DESIGN

This is an open-label, prospective, multi-center Phase II study for patients with metastatic well-to-moderately differentiated neuroendocrine tumors (including typical carcinoid and pancreatic neuroendocrine tumors) who are candidates for liver-directed radioembolization. Patients will receive treatment with lanreotide (120 mg subcutaneously [SQ] every 28 days) in combination with SIR-Spheres treatment (dose and treatment day to be determined by treating radiation oncologist). Patients who are currently receiving or have previously received lanreotide are eligible, and treatment with lanreotide can continue monthly until disease progression or unacceptable toxicity.

5.1 Treatment Plan

5.1.1 Lanreotide

Lanreotide 120 mg Day 1 of every cycle (every 28 days) by deep subcutaneous injection

Lanreotide will be given every 28 days, irrespective of when SIR-Spheres is administered. No waiting or adjusting of the schedule is required.

Radioembolization using SIR-Spheres Microspheres

Patients must be assessed with a hepatic angiogram and "break-through" scan to determine suitability for SIR-Spheres. These "mapping" procedures will be completed by the radiation oncologist 14-4 days prior to SIR-Spheres treatment.

Hepatic Angiogram

The patient will undergo a preliminary angiogram of the liver to determine the vascular anatomy of the liver. The hepatic angiogram will provide a road map of the arterial supply of the liver in order to plan delivery of the SIR-Spheres microspheres. The hepatic angiogram should be performed together with the "break-through" scan and results must be available prior to radioembolization with SIR-Spheres (see Appendix D).

Liver-Lung Break-Through Nuclear Scan

In order to mitigate the possibility of including patients who exhibit excessive liver-to-lung shunting a nuclear medicine "break-through" scan using ^{99m}Technetium (Tc) macroaggregated albumin will be performed in all patients prior to SIR-Spheres treatment.

If either the hepatic angiogram or the liver-lung break-through nuclear scan shows that a patient is ineligible to receive SIR-Spheres, then the patient will be removed from study.

5.1.2 SIR-Spheres Microspheres Administration

SIR-Spheres microspheres will be administered by a certified radiation oncologist, interventional radiologist, or nuclear medicine physician to the patient by injection through a trans-femoral catheter into the hepatic artery. All areas of tumor within the liver will be targeted with SIR-Spheres microspheres which usually involves treating both lobes of the liver. However, it is vital that the SIR-Spheres microspheres are not delivered to other organs such as the duodenum, stomach, pancreas, etc.

If metastases are present in both lobes, then it is preferable that SIR-Spheres treatment to both lobes be done during the same visit. If the metastases are limited to only one lobe, the radiologist can insert the catheter selectively into the lobar artery supplying only that lobe that contains the metastases. The SIR-Spheres microspheres will then be delivered only to the lobe containing the metastases with sparing of the other normal lobe. The SIR-Spheres microspheres are injected slowly into the hepatic artery to avoid reflux back down the hepatic artery and placement in the pancreas, stomach and other organs.

5.2 Study Duration

The end of the study is defined as the 12-month time point after the final patient is enrolled.

Patients will be evaluated for toxicity at the start of each cycle. Every 2 cycles, restaging will occur with imaging, laboratory chemistries, and tumor markers as defined in Appendix D. Patients will continue on treatment until progression as defined in Appendix E or intolerance to side effects.

5.3 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he is taking or has taken after the start of the study drug.

5.3.1 Permitted Concomitant Medications

Premedication with anti-emetics is allowed according to standard practice guidelines.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonate use, as recommended according to practice guidelines
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines
- Anticoagulation with coumarin-derivatives will not be permitted. However, a maximum daily dose of 1 mg will be permitted for port line patency. Should a thrombotic event occur while the patient is receiving treatment the patient may continue, but low molecular weight heparin (LMWH) will be the preferred treatment. However, other non-coumarin anticoagulants (Xarelto®) are acceptable.
- Lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when lanreotide treatment is initiated or when the dose is altered, and antidiabetic treatment should be adjusted accordingly. Patients who develop hyperglycemia during the study should be treated according to the American Diabetes Association guidelines.
- Concomitant administration of cyclosporine with lanreotide may decrease the relative bioavailability of cyclosporine and, therefore, may necessitate adjustment of cyclosporine dose to maintain therapeutic levels.
- Concomitant administration of bradycardia-inducing drugs (e.g., beta-blockers) may have an additive effect on the reduction of heart rate associated with lanreotide. Dose adjustments of concomitant medication may be necessary.

The pharmacological gastrointestinal effects of lanreotide may reduce the intestinal absorption of concomitant drugs. Limited published data indicate that concomitant administration of a somatostatin analog and bromocriptine may increase the availability of bromocriptine.

Vitamin K absorption was not affected when concomitantly administered with lanreotide.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator with the exception of those listed in Section 5.3.2.

5.3.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

5.3.3 Medications Affecting Metabolism via Cytochrome P450

The limited published data available indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that lanreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine; see Appendix F) should therefore be used with caution. Drugs metabolized by the liver may be metabolized more slowly during lanreotide treatment and dose reductions of the concomitantly administered medications should be considered.

6. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf), and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

6.1 Dose Modifications Due to Hematologic Toxicity

If hematologic toxicity occurs, hold all study drugs and re-evaluate in 1 week. Absolute neutrophil count (ANC) and platelets should be monitored weekly until recovery. If ANC and/or platelets do not recover within 3 weeks, the patient will be discontinued from the study.

Dose modifications on Day 1 of each cycle will be based on blood counts determined on the day of scheduled treatment. Nadir blood counts will not be used to determine dose modifications. Treatment on Day 1 of any cycle will proceed if blood counts demonstrate ANC >1500/µL and platelets>100,000/µL.

Table 1 Dose Modifications for Toxicities Suspected to be Related to Lanreotide

Toxicity	Grade	Actions
Non-hematological	1 or 2	Continue lanreotide therapy at full dose with optimal supportive care.
	3 or 4	Delay lanreotide until recovery to Grade ≤ 1 with optimal supportive care. If symptoms recur, discontinue the study.
Hematological	1 or 2	Continue lanreotide therapy at full dose, with optimal supportive care
	3 or 4	Delay study treatment until neutrophils ≥0.75 x10^9/L (750/mm^3), platelets ≥50 x10^9/L (50,000/mm^3) and Hgb ≥ 9.0 g/dL If toxicity recurs, discontinue the study.

6.2 Specific Recommendations for Management of Clinical Events Related to Lanreotide

6.2.1 Cholelithiasis and Gallbladder Sludge

Lanreotide may reduce gallbladder motility and lead to gallstone formation; therefore, patients may need to be monitored periodically.

6.2.2 Hyperglycemia and Hypoglycemia

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and other somatostatin analogues, inhibits the secretion of insulin and glucagon. Hence, patients treated with lanreotide may experience hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.

6.2.3 Thyroid Function Abnormalities

Slight decreases in thyroid function have been seen during treatment with lanreotide in acromegalic patients, though clinical hypothyroidism is rare (<1%). Thyroid function tests are recommended where clinically indicated.

6.2.4 Cardiovascular Abnormalities

In patients without underlying cardiac disease, lanreotide may lead to a decrease in heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to lanreotide treatment, sinus bradycardia may occur. Care should be taken when initiating treatment with lanreotide in patients with bradycardia.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix D.

The baseline physical examination, medical history, ECOG PS, electrocardiogram (ECG), complete blood counts (CBC), 3-part differential and platelets, comprehensive metabolic profile (CMP), and prothrombin time (PT)/partial thromboplastin time (PTT)/International Normalization Ratio (INR) should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. A pregnancy test must be performed within 72 hours of Cycle 1 Day 1. CT scans should be performed ≤28 days prior to initiation of treatment.

7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening:

- Written informed consent prior to any study-related procedures (≤28 days prior to initiation of treatment)
- Medical history
- Physical examination, measurements of height (first visit), weight, and vital signs (resting heart rate, blood pressure [BP], and oral temperature)
- Results of HIV, hepatitis B, and hepatitis C tests will be confirmed if taken within the past 1 year. If test results are >1 year old, patient will be required to provide a fresh blood sample for a new test.
- ECOG performance status (see Appendix A)
- 12-lead ECG
- Concomitant medication review
- CBC with 3-part differential and platelets
- CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (APT), AST, ALT, total bilirubin, total protein, and albumin.
- PT/PTT/INR
- Serum or urine pregnancy test (must be performed within 72 hours of Cycle 1 Day 1)
- CT scans of the chest, abdomen/pelvis ≤28 days prior to initiation of study treatment. If a CT scan is not possible, then an MRI may be used.

7.3 Study Treatment Assessments

7.3.1 Day 1 of each cycle

- Physical examination, including measurement of weight and vital signs
- ECOG performance status
- Adverse event (AE) assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets (may be done up to 72 hours prior to treatment)
- CMP (may be done up to 72 hours prior to treatment)

7.3.2 14 - 4 Days Prior to SIR-Spheres Cycle

The following tests will be obtained 14-4 days prior to SIR-Spheres treatment:

- Hepatic angiogram
- ^{99m}Tc MAA lung shunt scan

7.4 Response Assessment

It is recommended, but not required, for patients to have CT scans prior to and 6 weeks following treatment with SIR-Spheres. Patients will have CT scans performed 12 weeks after SIR-Spheres treatment.

After the post-SIR-Spheres 12-week scans, patients will be evaluated for response to treatment after every 2 cycles of lanreotide. The following assessments will be performed:

- CT scans of chest, abdomen and pelvis. If CT chest is normal at baseline this does not have to be repeated with each restaging unless there is a clinical reason to do so. If a CT scan is not possible, then an MRI may be used.

Patients with progressive disease or unacceptable toxicity should be discontinued from the study; patients with stable disease or response to therapy will continue treatment.

7.5 End of Study Treatment

The follow-up evaluations required after treatment ends due to completion of the planned study treatment period, disease progression, or once the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician are specified in Appendix D.

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End-of-Treatment Visit.

After withdrawal from or completion of protocol treatment, patients must be followed for AEs for 30 calendar days after the last dose of study drug. The following assessments will be performed:

- Physical examination, including measurement of weight and vital signs

- ECOG performance status
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP
- CT scans/MRI of chest, abdomen and pelvis (unless taken within the previous 8 weeks)

7.6 Follow-up

7.6.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression. Tests to be performed are listed in Appendix D. No follow up will be done for survival or if the patient starts a subsequent therapy.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 Lanreotide

Investigational Product	Dosage Form and Strength	Manufacturer
Lanreotide	120 mg	Ipsen Pharma Biotech

8.1.1 Labeling, Packaging, and Supply

Lanreotide is supplied in strengths of 60 mg/0.2 mL, 90 mg/0.3 mL, and 120 mg/0.5 mL in a single, sterile, prefilled, ready-to-use, polypropylene syringe (fitted with an automatic needle guard) fitted with a 20 mm needle covered by a low density polyethylene sheath.

Each prefilled syringe is sealed in a laminated pouch and packed in a carton.

NDC 15054-1060-3 60 mg/0.2 mL, sterile, prefilled syringe

NDC 15054-1090-3 90 mg/0.3 mL, sterile, prefilled syringe

NDC 15054-1120-3 120 mg/0.5 mL, sterile, prefilled syringe

Lanreotide must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light in its original package. Thirty (30) minutes prior to injection, remove sealed pouch of lanreotide from refrigerator and allow it to come to room temperature. Keep pouch sealed until injection.

Each syringe is intended for single use. Do not use lanreotide beyond the expiration date on the packaging.

8.1.2 Preparation and Administration of Lanreotide

Lanreotide is provided in a single-dose, prefilled syringe affixed with an automatic needle protection system. Inject lanreotide via the deep subcutaneous route in the superior external quadrant of the buttock. Alternate the injection site between the right and left sides from one injection to the next. Remove lanreotide from the refrigerator 30 minutes prior to administration. Keep pouch sealed until just prior to injection.

8.1.3 Precautions and Risks Associated with Lanreotide

Please refer to the prescribing information for information regarding precautions and risks associated with lanreotide (http://www.somatulinedepot.com/static/download/Somatuline%20Depot%20Full%20Prescribing%20Information.pdf).

8.2 SIR-Spheres® Microspheres

SIR-Spheres microspheres are to be administered in accordance with the terms of its marketing authorization and in accordance with institutional standard of practice. Please refer to the US Package Insert http://www.sirtex.com/us/clinicians/package-insert for detailed information on how to prepare and administer SIR-Spheres microspheres.

8.2.1 Labeling, Packaging, and Supply

Each site will procure a supply of SIR-Spheres microspheres, which is commercially available.

All study medications must be kept in a secure place under appropriate storage conditions. Storage conditions for SIR-Spheres microspheres can be found in the relevant US Package Insert. The product must not be used after the expiration date on the label.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.2.2 Preparation and Administration of SIR-Spheres® Microspheres

SIR-Spheres microspheres should be prepared and administered in accordance with information in the approved labeling.

8.2.3 Precautions and Risks Associated with SIR-Spheres® Microspheres

Please refer to the US Package Insert http://www.accessdata.fda.gov/cdrh_docs/pdf/P990065c.pdf for detailed information on the risks associated with the use of SIR-Spheres microspheres.

8.3 Accountability for Lanreotide

The Principal Investigator (or designee) is responsible for accountability of all used and unused lanreotide drug supplies at the site.

All lanreotide drug inventories must be made available for inspection by the Sponsor or its representatives and regulatory agency inspectors upon request.

At the end of the study, all Sarah Cannon Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the Sarah Cannon Innovations Regulatory Department. Lanreotide drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact Sarah Cannon Innovations regarding disposal of lanreotide.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al. 2009) (see Appendix E). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is an open-label, prospective, multi-center study for patients with metastatic well-to-moderately differentiated neuroendocrine tumors (including typical carcinoid and pancreatic neuroendocrine tumors) who are candidates for liver-directed radioembolization. Patients will receive treatment with lanreotide (120 mg monthly injections) in combination with SIR-Spheres treatment (dose and treatment day to be determined by treating radiation oncologist).

10.2 Sample Size Considerations

This study will test no formal hypothesis. The sample size of 25 patients is based on clinical practicalities rather than statistical reasoning, in order to evaluate the safety of administration of lanreotide and SIR-Spheres.

10.3 Analysis Population

The following analysis populations will be used:

- The Safety Analysis Set (SAF) / Safety Population is defined as all patients who have received at least one dose of both study medication, i.e. at least one dose of lanreotide (120 mg subcutaneously [SQ] every 28 days) and at least one dose of SIR-Spheres treatment

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures, will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to events endpoints will be reported using Kaplan-Meier estimates, with 95% confidence intervals (CI) for median time to event.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the Safety Analysis Set.

- Overall Response Rate (ORR) is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) (i.e., 2 CRs or PRs at least 4 weeks apart) according to the RECIST v1.1 criteria.

- Disease Control Rate (DCR) is defined as the proportion of patients with CR, PR or SD according to the RECIST v1.1 criteria.

    - For ORR and DCR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responder.

- Progression Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by the RECIST v1.1 criteria, or death on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment.

- Overall Survival (OS), defined as the time from the first day of study drug administration (Day 1) until death on study. Patients who are alive will be censored at the date of last known date alive.

For ORR and DCR, the estimates and the associated 95% CI (based on the Clopper-Pearson method) in each treatment group will be calculated. The absolute and relative difference in ORR and DCR between the two treatment groups will also be presented.

For PFS and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI be provided. The 95% CI for these endpoints will be calculated.

10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE v 4.03. A copy of the CTCAE scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term for all patients in the Safety Analysis Set. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented.

Other safety endpoints including laboratory results, vital signs and ECG findings will be summarized for all patients in the Safety Analysis Set.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary and they will be listed and summarized.

The safety analysis is the primary endpoint of this study.

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur 12 months after the last patient is enrolled.

10.5.2 Planned Interim Analysis

The safety data will be reviewed periodically after every 6 patients received treatment for 3 months.

10.5.3 Safety Review

The study will stop if Grade 3/4 treatment-related AEs are seen in ≥33% of patients.

10.5.4 Efficacy Review

There is no efficacy review planned.

10.6 Data Monitoring Committee

There is no Data Monitoring Committee (DMC) planned for this study.

10.7 Steering Committee

There is no Steering Committee planned for this study.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and Serious Adverse Events (SAEs), measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting SAEs to the Sarah Cannon Innovations Safety Department (see Section 11.2). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of that IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE**
- **Inpatient hospitalization of at least 24-hours 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 serious 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 hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes a serious adverse event (SAE) or not, any action taken (e.g., changes to study treatment), and outcome should be provided, along with the investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.0, and changes will be documented.

If the AE is serious, it should be reported immediately to Sarah Cannon Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms, abnormal test findings, changes in physical examination, hypersensitivity, and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

All adverse events (serious and non-serious) as well as special reporting circumstances, such as exposure via a parent during pregnancy or breast-feeding, overdose, medication error, misuse, abuse, off-label use or occupational exposure should be collected on the relevant eCRF where appropriate.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to lanreotide treatment (called study treatment), spanning from the start of study treatment until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating investigator as "serious", regardless of causality, require expeditious handling and reporting to Sarah Cannon Innovations Safety Department in order to comply with regulatory requirements. Determination of "life-threatening" or "serious" is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through 30 days after the last dose of study. **The Sarah Cannon Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to the Sarah Cannon Innovations Safety Department via fax or e-mail using the using the following contact information (during both business and non-business hours):

Sarah Cannon Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report. SAE reports will be sent to Ipsen Biopharmaceuticals, Inc. from the Sarah Cannon Innovations Safety Department within 24 hours of receipt of the SAE report by Sarah Cannon Innovations.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Sarah Cannon Innovations Safety Department as soon as it is available; these reports should be submitted using the Sarah Cannon Innovations SAE Report Form.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Sarah Cannon Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE to the Sarah Cannon Innovations Safety Department.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form, not available within the eCRF) should be completed and faxed to the Sarah Cannon Innovations Safety Department. The Sarah Cannon Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Sarah Cannon Innovations Safety Department. Sarah Cannon Innovations will forward the pregnancy form to Ipsen Biopharmaceuticals, Inc.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Sarah Cannon Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 Lanreotide Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Sarah Cannon Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of lanreotide, see the Investigator's Brochure.

11.4 Sponsor Serious Adverse Event Reporting Requirements

SAE and pregnancy information will be collected on the Sarah Cannon SAE Report Form and forwarded to Ipsen Biopharmaceuticals, Inc. Call Center, Fax: 866-792-7415 within 24 hours of Sarah Cannon Innovations Safety Department personnel becoming aware of the SAE.

Sarah Cannon Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations.

In addition, Ipsen Biopharmaceuticals and Sarah Cannon Development Innovations will report to the other significant safety or efficacy information (i.e., information that may affect the safety of patients in the Study or receiving the Study Drug in any other environment, such as, without limitation, commercial supply) immediately and within a maximum of 24 hours of identification of the information.

11.4.1 Sponsor Assessment of Unexpected

The Sponsor is responsible for assessing an adverse event or suspected adverse event as "unexpected."

An adverse event or suspected adverse reaction is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the current US Package Insert
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SARs that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation

When applicable, an unexpected adverse event may also apply to an event that is not listed in the current US Package Insert (USPI) or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events are suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the Investigator's Brochure or USPI), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the Package Insert or current IB.

11.4.2 Sponsor Reporting for Clinical Studies Under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the Sarah Cannon Innovations Safety Department must also be faxed to pharmaceutical company(ies) that are supporting the study with either funding or drug supply:

Ipsen Biopharmaceuticals, Inc. Call Center

Fax: 866-792-7415

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable study-related facilities. The investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the Sponsor's discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the Sponsor or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, informed consent form (ICF), IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all

subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for lanreotide will be prepared by the Sponsor or its representative as required for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered and approval of the appropriate regulatory bodies obtained prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICF).

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF that includes the patient's signature will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information

- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Sarah Cannon Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub investigator, Sarah Cannon Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between Sarah Cannon Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representatives. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, or addition or removal of new tests or procedures shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed, or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment approval from IRB and/or FDA or other regulatory authorities include, but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and/or procedures
- Addition/removal of a new Investigator

It should be further noted that if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Innovations
Regulatory Department
1100 Charlotte Avenue, Suite 800
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study

- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of Sarah Cannon Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to: hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity; and batch/code or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records including the identity of all participating patients (sufficient information to link records; e.g., eCRFs, medical records), all original, signed ICFs; and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by the Sponsor (Sarah Cannon Innovations) throughout the study, and will be held by the Sponsor at the conclusion of the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Sarah Cannon Innovations and replaced instead with the patient number and patient's initials. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the Investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multicenter study and agrees that any publication by the Investigator of the results of the study conducted at research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the Investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Sarah Cannon Innovations Confidential Information from all publications.

15. REFERENCES

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Caplin, M. E., Pavel, M., Ćwikła, J. B., et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. New Eng J of Med 2014: 371, 224-233.

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Kennedy, A., Coldwell, D., Sangro, B., et al. Integrating radioembolization into the treatment paradigm for metastatic neuroendocrine tumors in the liver. Am J Clin Oncol 2012: 35, 393-398.

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Kennedy, A., Coldwell, D., Sangro, B., et al. Radioembolization for the treatment of liver tumors general principles. Am J Clin Oncol 2012: 35, 91-99.

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Kennedy, A. S., Dezarn, W. A., McNeillie, P., et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. Am J Clin Oncol 2008: 31, 271-279.

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King, J., Quinn, R., Glenn, D. et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer 2008: 113, 921-929.

16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 3 months after stopping treatment.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Male Partner Sterilization When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS) or established use of oral, injected or implanted hormonal methods of contraception.

b) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of child-bearing potential must use condoms plus spermicidal agent during the study treatment period and for 3 months after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom

- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to the Sarah Cannon Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the **Sarah Cannon Innovations Safety Department**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

Appendix D: Schedule of Assessments

Procedures	Screening	Lanreotide Every cycle	SIR-Spheres TBD	Restaging Every 2 cycles	End of Treatment[i]	Follow-Up
	Baseline	Day	Day			Prior to Disease Progression[j]
		1	TBD			
TESTS & OBSERVATIONS						
Informed Consent[a]	X					
Medical history	X[b]					
Physical examination, vital signs, height, weight[c]	X[b]	X			X	X
ECOG Performance Status	X[b]	X			X	X
12-lead ECG	X[b]					
HIV/HBV/HCV Tests/Results	X[b]					
Adverse event evaluation		X			X	X
Concomitant medication review	X	X			X	X
LABORATORY TESTS						
CBC, including 3-part differential and platelets	X[b]	X			X	X
CMP[d]	X[b]	X			X	X
PT/PTT/INR[e]	X[b]					
Serum or urine pregnancy test[f]	X					
DISEASE ASSESSMENT						
CT scan/MRI of the chest, abdomen, pelvis[g]	X			X[g]	X	X
Hepatic angiogram			X			
^{99m}Tc MAA lung shunt scan[h]			X			

Appendix D: Schedule of Assessments (continued)

a Informed Consent must be obtained ≤28 days prior to the initiation of study treatment.

b Baseline procedures including medical history, physical examination, ECOG PS, 12-lead ECG, CBC, CMP, and PT/PTT/INR should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. Also at screening visit, treating physician will confirm results of HIV, hepatitis B, and hepatitis C tests if taken within the past 1 year. If results >1 year old, patient must provide a fresh blood sample for a new test.

c Physical examination will include measurements of height (pretreatment visit only), weight, and vital signs (resting heart rate, blood pressure, and temperature).

d CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin. CMP may be done up to 72 hours prior to treatment.

e If PT/PTT/INR are normal at baseline they do not need to be repeated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have coagulation tests performed according to standard practice guidelines.

f Serum or urine pregnancy tests are to be conducted in women of childbearing potential within 72 hours of Cycle 1 Day 1.

g CT scans of the chest, abdomen/pelvis ≤28 days prior to initiation of treatment. It is recommended, but not required, for patients to have CT scans prior to and 6 weeks following treatment with SIR-Spheres. Patients will have CT scans performed 12 weeks after SIR-Spheres treatment. After the post-SIR-Spheres 12 week scans, patients will be evaluated for response to treatment after every 2 cycles of lanreotide. The following assessments will be performed: CT scans of chest, abdomen and pelvis. If CT chest is normal at baseline this does not have to be repeated with each restaging unless there is a clinical reason to do so. If a CT scan is not possible, then an MRI may be used.

h Patients will be at assessed 14-4 days prior to SIR-Spheres treatment to determine the suitability for SIR-Spheres (see Section 7.3.2)

i All patients will undergo the End of Treatment visit assessments listed within 30 days after treatment ends due to completion of the planned study treatment period, or once a patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End of Treatment visit. After withdrawal from or completion of protocol treatment, patients must be followed for AEs for 30 calendar days after the last dose of study drug.

j Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression. PFS will be evaluated for this trial 6 and 12 months after the last patient is enrolled. No follow up will be done for survival or if the patient starts a subsequent therapy.

Appendix E: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Definitions

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.

Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

Guidelines for Evaluation of Measureable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.
Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
Ultrasound:	When the primary study endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters..

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).

Stable Disease (SD): Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the subject also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

As detailed above, the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for studies in which response rate is the primary endpoint, but is not required in randomized studies or studies with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

Appendix F: Common Substrates for CYP3A

The following list describes medications which are common substrates for CYP3A. This list should not be considered all-inclusive.

CYP3A Substrates with Narrow Therapeutic Index
Alfentanil
Astemizole
Cisapride
Cyclosporine
Dihydroergotamine
Ergotamine
Fentanyl
Pimozide
Quinidine
Sirolimus
Tacrolimus
Terfenadine

Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classSub (September 19, 2015)