Amendment

Protocol Number: 13C0193-J **Reference Number:** 373860

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Protocol Title: Evaluation of 68Gallium- DOTATATE PET/CT for Detecting Primary and Metastatic Neuroendocrine Tumors

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* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

Abbreviated Title: 68Gallium Detecting Tumors

CC Protocol #: 13-C-0193J

Version Date: 09/20/2017

NCT Number: NCT01967537

Title: Evaluation of ^{68}Gallium- DOTATATE PET/CT for detecting Primary and Metastatic Neuroendocrine Tumors

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Investigator Roles:

A. Obtain information by intervening or interacting with living individuals for research purposes

B. Obtaining identifiable private information about living individuals

C. Obtaining the voluntary informed consent of individuals to be subjects

D. Makes decisions about subject eligibility

E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes

F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes

G. Some/all research activities performed outside NIH

Investigational Agents:

Drug Name:	DOTATATE
IND Number:	119098
Sponsor:	PET department, NIH
Manufacturer:	PET department, NIH

PRÉCIS

Background:

- Neuroendocrine tumors (NETs) are rare malignancies occurring in the gastrointestinal tract, islets of the pancreas, lung, adrenal medulla and thyroid C-cells.
- Their incidence has increased over the last decade, with an incidence of 6 per 100,000 persons a year and they represent 0.46% of all malignancies.
- Most NETs are sporadic, but they can be part of familial cancer syndromes such as multiple endocrine neoplasia type 1 (MEN1), MEN2, and neurofibromatosis type 1 (NF1) or Von Hippel-Lindau (VHL) syndrome.
- Surgical resection remains the only curative treatment option for patients with NETs but 80% of patients are diagnosed with advanced (metastatic, locally inoperable, or recurrent) disease.
- The main prognostic factor in patients with NET is the extent of disease.
- The best imaging technique for detecting unknown primary and metastatic NETs has yet to be determined.
- NET cells express somatostatin receptors that can be targeted with radiolabeled ^{68}Gallium-DOTATATE (Octreotate) for imaging purposes.
- The primary goal of this protocol is to determine the accuracy of a new somatostatin receptor targeted imaging technique, using ^{68}Gallium-DOTATATE PET/CT to detect unknown primary and metastatic NETs.

Objective:

- To determine the accuracy of ^{68}Gallium-DOTATATE PET/CT scans in detecting unknown primary and metastatic gastrointestinal and pancreatic neuroendocrine tumors.

Eligibility:

- Patients with
    - suspicion of NET on axial imaging (CT/MRI/FDG PET) and/or
    - biochemical evidence of NET (serum/urinary) based on elevated levels of chromogranin A, pancreatic polypeptide, neuron-specific enolase, vasoactive intestinal polypeptide, serotonin (urinary 5-HIAA), gastrin, somatostatin, catecholamines, metanephrines, calcitonin, fasting insulin, C-peptide (proinsulin), glucagon and/or
    - familial predisposition to NET in patients with MEN1 and VHL.
- Age $\geq$ 10 years of age.
- Patients must be willing to return to NIH for follow-up.

Design:

- Prospective study.
- A ^{68}Ga-DOTATATE PET/CT scan will be done in patients with suspicious lesions, unknown primary tumor or metastatic gastrointestinal or pancreatic neuroendocrine

disease found on anatomic imaging (CT/MRI) or in patients having biochemically active disease.

- Both functional and non-functional solid tumors will be included in this study. Furthermore, asymptomatic and symptomatic, sporadic and familial cases of NETs (such as VHL, MEN1) will be included.
- Demographic, clinical and pathologic data will be collected from the medical record and patient interview for each patient. Data will be stored in a computerized database.
- After their initial on-study evaluation, patients will be staged according to findings on imaging studies with respect to primary tumor site, size and metastases. Surgical resection of NET and/or medical managements will be recommended based on standard practice guidelines. In patients who undergo surgical treatment, the samples will be immediately stored until molecular analysis.
- Follow up will be done yearly for a total duration of 5 years. This includes a yearly imaging study and a biochemical and clinical evaluation, to assess tumor growth and disease progression.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine the accuracy of ^{68}Gallium-DOTATATE PET/CT scans in detecting unknown primary and metastatic gastrointestinal and pancreatic neuroendocrine tumors.

1.1.2 Secondary Objectives

- To evaluate ^{68}Gallium-DOTATATE uptake in NETs and its association with tumor differentiation.
- To determine whether ^{68}Gallium-DOTATATE uptake value is predictive of tumor growth and/or disease progression.
- To determine the relation between somatostatin receptor status in tumor samples and ^{68}Gallium-DOTATATE uptake.
- To evaluate the feasibility of radio-guided surgery in NETs using ^{68}Gallium-DOTATATE.

1.2 BACKGROUND AND RATIONALE

Neuroendocrine tumors (NETs) are a diverse group of malignancies occurring in the gastrointestinal tract, pancreas islets, lung, pancreas, adrenal medulla, thyroid C-cells, parathyroid, and anterior pituitary. Their incidence has increased over the last decade, with a current incidence of about 6 per 100,000 persons a year and a prevalence of 35 per 100,000 persons [1, 2]. NETs are relatively rare tumors and represent 0.46% of all malignancies, with an average age at diagnosis of 61.4years [3, 4].

Most NETs are sporadic, but they can be part of familial cancer syndromes such as multiple endocrine neoplasia type 1 (MEN1), MEN2, and neurofibromatosis type 1 (NF1) (e.g., gastrin-producing G-cell tumors and somatostatin-producing D-cell tumors of the duodenum) [5-7] or Von Hippel-Lindau (VHL) syndrome [8]. Patients with MEN1 and VHL are at risk of developing benign or malignant NETs in the pancreas, small intestine, adrenal and lung.

Neuroendocrine cells are the largest group of hormone-producing cells in the body. At least 13 distinct gut neuroendocrine cells exist, all of which may oversecrete various bioactive peptides or amines including serotonin, somatostatin, histamine, and gastrin, which result in significant morbidity and mortality.

A unique feature of NETs is the frequent expression of somatostatin receptors (SSTR) in the tumor cells. There are five different SSTR subtypes; more than 70% of NETs of both the GI tract and pancreas express multiple subtypes, with a predominance of receptor subtype 2 [sst(2)] and receptor subtype 5 [sst(5)] [9, 10]. These receptors can be targeted with radiolabeled peptides for imaging and treatment [11].

NETs are heterogeneous in their clinical presentation and malignant potential. The tumors are classified by their functional status based on hormone hypersecretion, which can result in

significant clinical symptoms such as flushing, diarrhea, hypoglycemia, gastric ulcers or skin rash. Carcinoid syndrome, which occurs in up to 20% of patients with NETs, is associated with flushing, abdominal pain, diarrhea, bronchoconstriction, and carcinoid heart disease.

Clinical presentation, thus, depends on the site of the primary tumors, the aggressiveness of tumor growth, and whether the tumor is functioning and produces symptoms. Most NETs are non-functioning and present fairly late, with symptoms of mass effect or distant (usually hepatic) metastases, or both. Delay in diagnosis is typical (5–7 years on average) in patients with NETs, increasing the probability of metastatic disease [12], especially for NETs of the intestines and pancreas. The identification of metastatic disease represents the most important prognostic factor after tumor grading for NETs [4, 13]. According to data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, 49% of NETs are localized, 24% show regional metastases, and 27% are associated with distant metastases [4]. In addition, disease stage is also associated with the location of the primary tumor site at initial diagnosis. For example, distant metastases were present in 64% of pancreatic NETs, followed by cecal, colonic and small intestinal NETs in 44, 32 and 30% of cases, respectively [4]. The most frequent sites of metastases are the liver, followed by the peritoneum, lung, and bone [3].

NETs are classified according to histopathological findings by the 2010 WHO classification for the degree of tumor differentiation [14], with specific features based on tumor site of origin. With respect to Ki67 proliferation index, cutoff values for grading are G1: Ki67<2%; G2: Ki67=3-20%; G3: Ki67>20%. This classification categorizes NETs into well- and moderately-differentiated tumors (NET G1/G2), and poorly differentiated carcinomas (NEC G3). This staging system accurately predicts patient prognosis. Factors that determine the clinical course and outcome of patients with NETs are complex and multifaceted, they include the following [4, 15]:

- The site of origin.
- Hormone secretory properties.
- The size of the primary tumor.
- The extent of disease.
- Grade based on Ki-67 staining.

Surgical resection remains the only curative treatment option for patients with NETs [16]. However, the clinical applicability of surgery is limited, as 80% of patients are diagnosed with advanced (metastatic, locally inoperable, or recurrent) disease. Palliative surgery may be warranted as tumor removal may relieve symptoms without excessive morbidity from the procedure. Tumor debulking surgery (removing at least 90% of the tumor) may also be an option for isolated metastasis when it is resectable along with the primary tumor. In cases of liver metastases, complete resection is associated with better long-term survival [17], and survival rates of 60-80% at 5 years may be achieved.

As stated above, reduction of tumor burden comprises of removal of the primary tumor, regional lymph nodes and resectable liver metastases. Reoperations for recurrent and metastatic lesions may be challenging because some lesions may be difficult to pinpoint during the operation due to their size, and the presence of multiple adhesions and altered anatomy. Thus, reoperation can be

difficult for surgeons to accurately differentiate scar and inflammatory tissue from malignant tissue (**Figure 1**A).

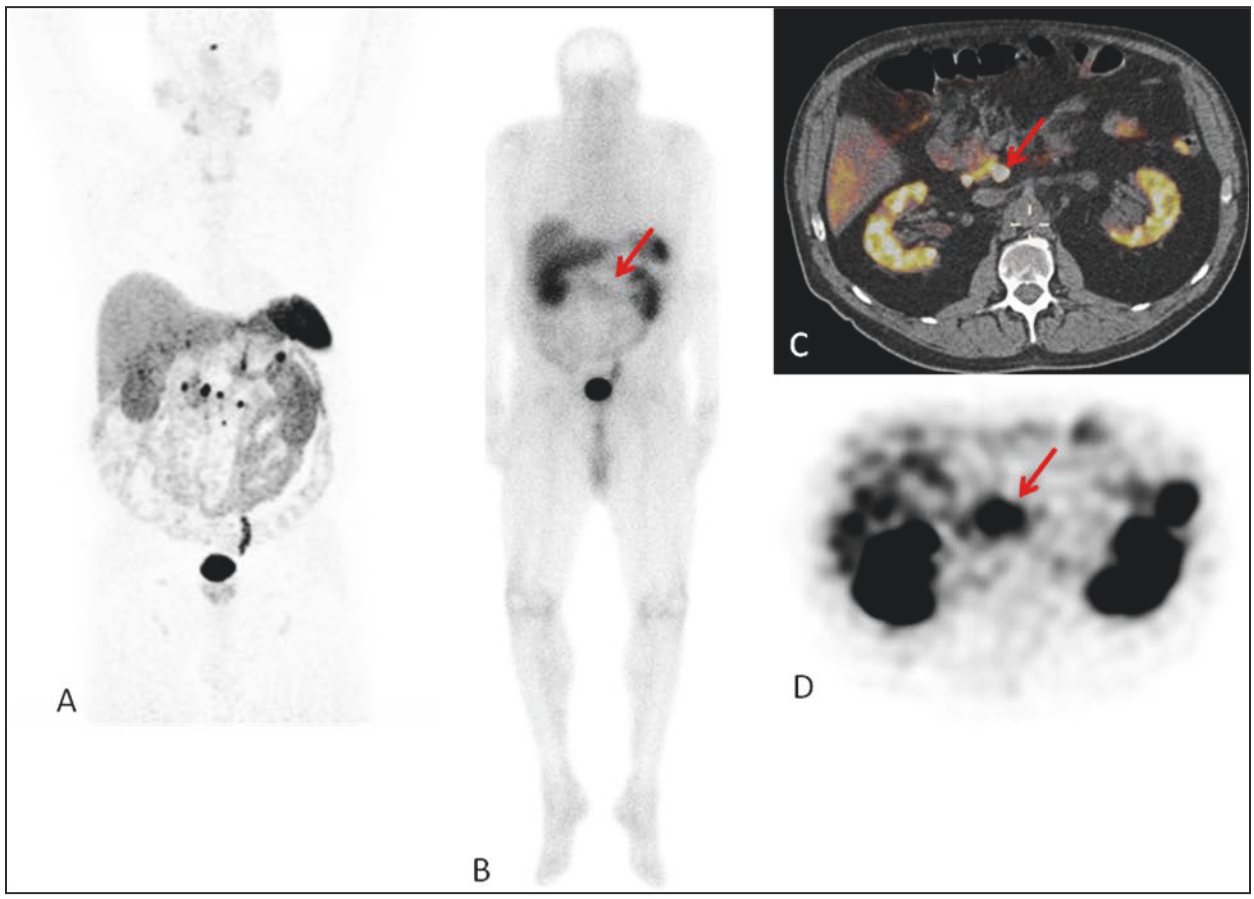


Figure 1. Comparison of ^{68}Gallium-DOTATATE PET and Octreo SPECT in a patient with metastatic neuroendocrine tumor and unknown primary tumor who had exploratory laparotomy and resection of a mesenteric root NET one year prior.

Figure 1A and C: DOTATATE PET/CT showing the exact locations of 7 retro-peritoneal lesions with the largest having SUVmax of 85 (arrow in **Figure 1**C).

Figure 1B and D: Octreo SPECT showing an octreotide positive abnormality in the upper abdomen (arrows).

Radio-guided surgery is an intraoperative localizing technique using target-specific radiotracers injected before surgery that accumulates in the targeted tissues that is standard of care for sentinel lymph node localization in patients with melanoma and breast cancer. In NETs, the use of radio-guided surgery with handheld gamma probes has been shown to be possible, using ^{99m}Tc-labeled somatostatin analogues such as [^{99m} Tc-EDDA/HYNIC] octreotate [18], or positron emitter labeled compounds such as ^{18}F-deoxyglucose (FDG) [19] and,^{68}Gallium-DOTANOC or DOTATATE (Octreotate) [20]. Specifically, a recent pilot study using ^{68}Gallium-

DOTATATE in nine patients showed that the gamma probe detected 94% of the histologically quantified lesions, whereas PET/CT detected 69% of the lesions and surgical palpation 50% of the lesions [20]. Both studies using somatostatin-analogues were in small sample size, comprising 9 patients each and its widespread use and feasibility will need further validation in a larger cohort.

Medical treatment for NETs has two aims: amelioration of symptoms and suppression of tumor growth and spread. Symptom relief can be achieved with somatostatin analogues (octreotide). In patients with locally inoperable or metastatic disease, octreotide LAR has shown to inhibit tumor growth, whether the tumors are functionally active or inactive (PROMID Study Group) [21]. Furthermore, everolimus (mTOR inhibitor) with octreotide LAR treatment has shown to have better outcome for progression-free survival in patients with advanced NETs in a randomized clinical trial (RADIANT-2) [22]. In patients with failed octreotide LAR treatment, chemotherapy or hepatic chemoembolization, the combination of capecitabine (antimetabolite) and temozolomide (alkylating agent) achieved a response rate of 61% [23].

For tumor suppression, chemotherapy and a newer treatment referred to as "peptide receptor radionuclide therapy" have been used [24]. This radiotherapy uses radiolabeled somatostatin (cytotoxic drug) targeting somatostatin receptors which are overexpressed in NETs and have been reported to have efficacy in patients with metastatic NETs [25]. The lutetium-based peptides have shown few side effects and resulted in median progression-free survival of more than 40 months in patients with metastatic NETs [26]. However, the amount and subtype of SSTR expression in tumor samples and the number of clinically positive tumors in order to detect and ablate them is poorly understood.

The primary goal of the present protocol is to determine the accuracy of a new somatostatin receptor targeted imaging technique to detect NETs. Thus, the goals of the proposed study are to determine the accuracy for diagnosing of primary sites of NETs, to define the characteristics of those lesions in regards to size, localization and aggressiveness, to determine the accuracy for detecting metastatic disease, and perform correlative molecular analysis to determine if the presence, expression level and subtypes of SSTR influence imaging results.

Computed tomography (CT) has been the most widely used modality with the best sensitivities when both arterial and portal venous phases are performed for detecting pancreatic and intestinal NETs. Magnetic resonance imaging (MRI) is less accurate, identifying >50% of pancreatic NETs larger than 3cm in diameter but only 5% if the tumor was smaller than 1cm [27, 28].

Recent studies suggest functional imaging with positron emission tomography (PET) is helpful as a localizing modality. For example, ^{18}FDG PET scans have been reported to be helpful for localizing and for possibly distinguishing malignant from benign NETs [29, 30]. However, ^{18}FDG PET scans have limited use in well-differentiated NETs due to the low expression of glucose transporters and low proliferative activity in these tumors [31-33]. In fact, in our prospective study of patients with VHL and solid pancreatic lesions on axial imaging, ^{18}FDG-PET only identified approximately half (46%) of the pancreatic NETs diagnosed on CT and MRI [34].

Newer functional imaging studies have emerged targeting the somatostatin receptor which is expressed in over 70% of NET cells. The current gold standard functional imaging technique for NETs is octreotide scintigraphy, targeting the somatostatin receptor 2, but with variable

diagnostic sensitivity according to tumor site of origin, 65-100% [35, 36]. Up to five different somatostatin receptor subtypes have now been identified and studies show that gastrointestinal NETs have high expression of somatostatin receptor 2 [11, 37].

The expression of somatostatin receptors enables new imaging techniques using PET/CT with radioactively labeled somatostatin analogs such as ^{68}Gallium-DOTATATE (Octreotate) [38]. ^{68}Gallium-DOTATATE PET scanning may have several advantages over octreotide scintigraphy: a shorter procedure (as scintigraphy results are available only within 24-48h), lower cost [39], lower radiation dose and better diagnostic accuracy due to the higher affinity of ^{68}Gallium analogs for somatostatin receptor 2 as well as higher spatial resolution with PET [40-42]. Interim analysis results as detailed in the statistical section show that ^{68}Gallium-DOTATATE PET/CT to be far superior to Octreoscan in detection of disease. Clinically management has changed due to the utilization of this scan. In addition, ^{68}Ga-DOTATATE is a generator produced and therefore cyclotron independent PET tracer, allowing for a lower cost and wider usage overall in the NET patient population.

Localization of primary tumors and detection of metastases are crucial for optimizing treatment strategies. Slow-growing PNETs are best treated by complete surgical removal, but in the presence of metastases or non-resectable disease, unnecessary surgery could be spared. Furthermore, PET with ^{68}Ga-labeled somatostatin ligands has been used as a tool in localizing unknown primary tumor in metastatic NET [43]. According to *Hofman et al.* [44], ^{68}Ga-PET was superior than octreoscan and conventional imaging (CT, MRI, bone scintigraphy) in identification of additional sites of disease, with bone and local lymph nodes being the most frequent sites. Furthermore, PET with ^{68}Ga-labeled somatostatin has been suggested to be superior to FDG PET and FDOPA PET in the detection of additional tumors [38, 45, 46]. *Frilling et al.* [47] showed SSRT- ^{68}Ga -PET/CT to be superior to CT and/or MRI, as it detected additional hepatic and/or extrahepatic metastases in 22 of 33 patients. It has been recommended as a diagnostic modality by the European Neuroendocrine Tumor Society 2012 [48], and provides staging by assessing metastases that can lead to changes in both medical and surgical management strategies [44, 47]. Although, ^{68}Ga-labeled somatostatin scintigraphy is emerging as an accurate diagnostic imaging approach, most studies in Europe are in relatively small study cohorts or retrospective. Therefore, we propose to study the accuracy of ^{68}Ga-DOTATATE imaging in patients with NET with the primary goal of determining if this modality can be used to detect unknown primary NET and can detect malignant/metastatic disease in patients with NETs. We will correlate radiologic findings of ^{68}Gallium-DOTATATE PET/CT to results obtained by anatomic imaging (CT/MRI) and pathologic confirmation in those patients undergoing surgical treatment. This will determine whether additional lesions can be found on ^{68}Gallium-DOTATATE PET/CT.

Furthermore, we will analyze somatostatin receptor status in tumor samples in patients who have surgical treatment using immunohistochemistry and Western blot analysis for protein expression [49] and quantitative RT-PCR for mRNA expression. Receptor status in tissue samples will then be correlated to ^{68}Gallium-DOTATATE PET uptake status in the same lesion, which is specific to somatostatin receptor 2 [50]. With this information on receptor status of the lesions and ^{68}Gallium-DOTATATE PET uptake, the feasibility of using this agent in the future for treatment of patients with metastatic NETs could also be determined.

Additionally, we will collect research blood and urine at baseline in order to perform proteomics using Mass spectrometry for the discovery and validation of biomarkers. Recent advances have shown blood and urine markers could be identified by mass spectrometry in a variety of cancers (bladder, renal, ovarian, breast, colorectal) [51, 52]. Serum proteomics has been used to find biomarkers in gastric cancer [53], prostate cancer [54] and lung cancer [55].

As discussed previously, NETs can be functional and secrete hormones into the circulation, leading to the development of clinical symptoms. They are thought to be due to the release of serotonin and peptides. Chromogranin A is a biochemical marker in the circulation currently used for monitoring and screening of NETs. However, this marker has been shown to be in the normal range for certain patients even though they present with clinical symptoms like flushing. Moreover, we have seen patients who have marked symptoms of flushing and diarrhea but with normal levels of vasoactive hormones on our screening, which suggests there are vasoactive hormones present that are unknown. As an example, a recent study demonstrated MAC2 to be secreted by proteomes of neuroendocrine cell lines and the same marker to be elevated in seven patients with NET, and could be identified as a potential biomarker for NET [56]. With the collection of serum and urine samples for proteomic analysis in our patient cohort, we could help identify new biomarkers for the screening and monitoring of NETs that do not have elevation in known vasoactive hormones.

Further, demonstration of pre-operative ^{68}Gallium-DOTATATE PET uptake in tissue can be used as an adjunct localization technique to surgical ultrasound or palpation during surgery. Using a handheld gamma probe that localizes the target specific radiotracers that accumulate in NETs, additional occult tumors and microscopic disease could be detected, thereby improving the surgical treatment and the final outcome of patients. Previous studies using ^{68}Gallium-analogues were in small sample size and need further validation. We will use the gamma probe at the time of operation to determine the feasibility and accuracy for detecting NETs intra-operatively and for confirming removal of all tumors seen on preoperative ^{68}Gallium-DOTATATE PET scans by giving those patients who require an operation a trace dose before their operation.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients with any one of #1, #2, and/or #3:

1. Suspicion of NET on axial imaging (CT/MRI/FDG PET) and/or
2. Biochemical evidence of neuroendocrine tumor (serum/urinary) based on elevated levels of chromogranin A, pancreatic polypeptide, neuron-specific enolase, vasoactive intestinal polypeptide, serotonin (urinary 5-HIAA), gastrin, somatostatin, catecholamines, metanephrines, calcitonin, fasting insulin, C-peptide (proinsulin), glucagon and/or
3. Familial predisposition to NET in patients with MEN1 and VHL (symptomatic and/or asymptomatic cases; with biochemical or anatomic imaging evidence of disease).

2.1.1.2 Age ≥10 years of age.

2.1.1.3 For females: Negative urine pregnancy test OR post-menopausal for at least 2 years OR patient has had a hysterectomy.

2.1.1.4 Patients must be willing to return to NIH for follow-up.

2.1.1.5 Ability of subject or Legally Authorized Representative (LAR) (if the patient is deemed by the treating physician to be cognitively impaired or questionably impaired in such a way that the ability of the patient to give informed consent is questionable) to understand and the willingness to sign a written informed consent document indicating that they are aware of the investigational nature of this study.

2.1.2 Exclusion Criteria

2.1.2.1 Patients unwilling to undergo serial non-invasive imaging.

2.1.2.2 Pregnant or lactating women: Pregnant women are excluded from this study because the effects of ^{68}Ga-DOTATATE in pregnancy are not known. Because there is an unknown but potential risk for adverse events in nursing infants secondary to administration of ^{68}Ga-DOTATATE in the mother, breastfeeding should be discontinued for at least one day if the mother receives ^{68}Ga-DOTATATE.

2.1.2.3 Patients that have recognized concurrent active infection,

2.1.2.4 Patients with the use of any investigational product or device, excluding F-DOPA scans, within 30 days prior to dosing.

2.1.3 Recruitment Strategies

The study will be posted on the CCR website and on clinicaltrials.gov.

2.2 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

3 STUDY IMPLEMENTATION

3.1 ON STUDY EVALUATION

A ^{68}Ga-DOTATATE PET/CT scan will be done in patients with suspicious lesions, unknown primary tumor or metastatic gastrointestinal or pancreatic neuroendocrine disease found on anatomic imaging (CT/MRI) or in patients having biochemically evidence of disease. Both functional and non-functional solid tumors will be included in this study. Patients with any type

of tumor grade will be included (well and/or poorly differentiated). Furthermore, asymptomatic and symptomatic, sporadic and familial cases of NETs (such as VHL, MEN1) will be included.

We will enroll patients that are currently participating in protocols at NIH for MEN1 and VHL syndrome.

The ^{68}Ga-DOTATATE PET/CT will be performed as a SPECT/CT, to assess its accuracy in detecting and staging of NETs.

3.1.1.1 Detailed demographic data will be collected from the medical record and patient interview for each patient participant. Data will be securely stored in a computerized database.

3.1.1.2 Non-invasive imaging

- CT scan with contrast of the chest, abdomen and pelvis.
  Tridimensional tumor measurements will be performed on contrast CT scans to evaluate size and rate of tumor growth, on scans obtained at baseline and at each follow up visit.
- Patients with a severe iv contrast allergy (anaphylaxis with premedication) will have a MRI of the abdomen and pelvis performed and non-contrast CT of Chest instead of the CT scan (MRI of chest will only be performed if suspicious lesions seen on previous imaging or on ^{68}Gallium-DOTATATE PET/CT.
- ^{68}Gallium DOTATATE PET/CT scan for gastrointestinal or pancreatic NET.

3.1.1.3 Laboratory evaluations

- CBC with differential
- Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, Total CK, Uric Acid
- Chromogranin A, serotonin (urinary 5-HIAA), calcitonin.

3.1.1.4 Patients on octreotide treatment for symptomatic NETs

Octreotide acetate therapy will be continued. Studies have shown no significant change in SUV uptake related to octreotide acetate treatment [57].

3.1.1.5 Research blood and urine (see section **4.1**).

3.2 FOLLOW-UP EXAMINATIONS

Scheduling of follow up evaluations will be coordinated by the EOB research nurse.

Patients with known or suspicion for having NETs may undergo the following evaluations yearly:

- CT scan of the abdomen and pelvis with contrast.
- In some patients with increasing number of lesions, biochemical evidence of persistent disease not seen on anatomic studies, increase in size of lesions or with small lymph node lesions (**Figure 2**) that are only seen on ^{68}Gallium DOTATATE PET/CT scan, a follow up scan will be performed at one year and yearly, up to 5 years from study enrollment.

- For patients who have functioning tumors (if elevated at baseline or as clinically indicated):
    - Fasting insulin and glucagon, vasoactive intestinal polypeptide (VIP), pancreatic polypeptide, neuron-specific enolase, serotonin (urinary 5-HIAA), catecholamines, metanephrines
    - Fasting chromogranin A
    - Fasting gastrin

Follow-up will be done for a total of five years.

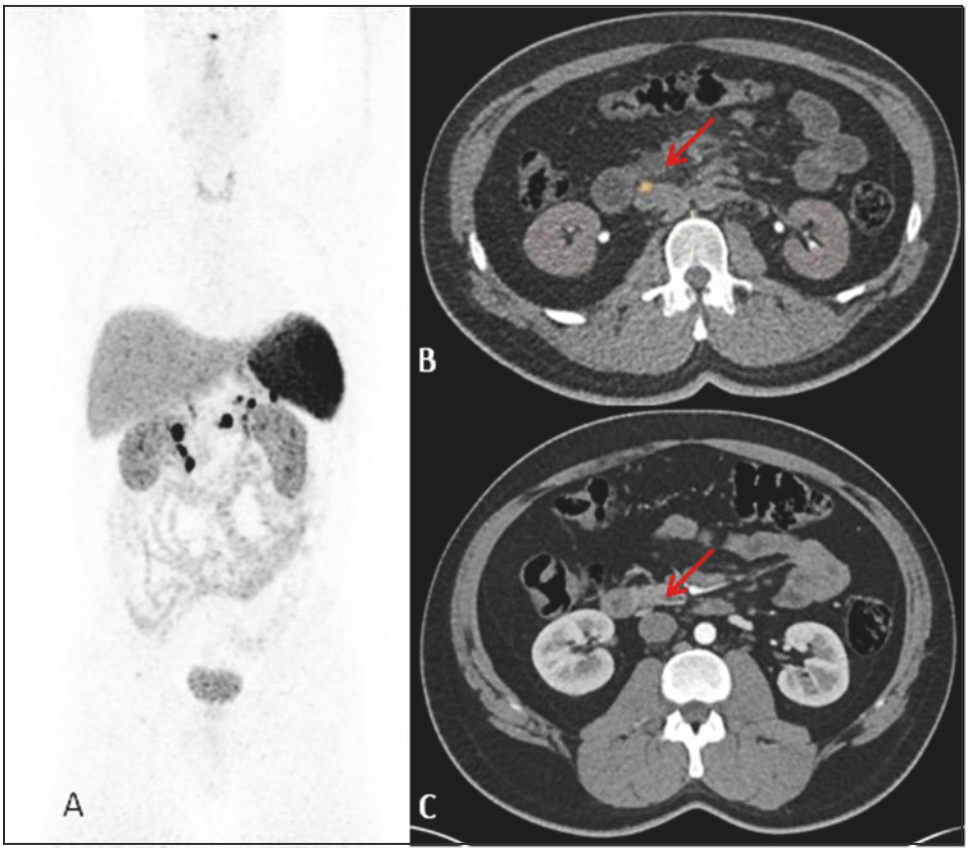


Figure 2 Example of a patient with MEN-1, 32 year old male, who has known pancreatic lesions, and was found to have a retropancreatic lymph node on ^{68}Gallium-DOTATATE PET/CT (SUV_{max} 79) (Figure 2A and B, arrow). This lesion was not clearly visible and not described as abnormal on a pancreatic protocol CT scan (Figure 2C, arrow) and would be difficult to follow.

In cases, with small lesions, a follow-up ^{68}Gallium-DOTATATE PET/CT will be helpful to recognize possible metastatic lymph nodes and to evaluate disease progression.

3.3 STUDY CALENDAR

	Screening	Baseline Day of PET/CT	Dose	PET/CT Imaging	Yearly Follow-Up
Informed consent	•				
Study entry criteria	•				
Demographic information	•				
Medical history and concurrent diseases	•				
Prior/concomitant medication	•				
Physical examination	•				•
Vital signs[a]	•				•
Blood samples	•[b]				•[c]
AE Monitoring/Query					•

	Screening	Baseline Day of PET/CT	Dose	PET/CT Imaging	Yearly Follow-Up
^{68}Ga-DOTATATE administration[d]			•		•[e]
^{68}Ga-DOTATATE PET/CT Imaging				•	• [e]
CT Imaging[f]	•				•
Correlative Research Studies		•[g]			
Advance Directive [h]	•				

[a] Vital signs: Heart rate, blood pressure, respiratory rate, temperature, pulse oximetry (according to Appendix A and B).

[b] At screening: CBC with differential/ Full chemistry/ Neuroendocrine peptides (as cited in section **3.1.1.3**)/ Pregnancy test if required.

[c] At yearly follow-up if functional tumors: Fasting insulin, glucagon, VIP, pancreatic polypeptide, neuron specific enolase, urinary 5-HIAA, catecholamines, metanephrines, fasting chromogranin A fasting gastrin

[d] Administration of about 5mCi of the ^{68}Ga-DOTATATE intravenously.

[e] To be performed at the one year follow up time point and up to 5 years from study enrollment in certain patients only.

[f] To be performed within ± 6 months of the ^{68}Ga-DOTATATE PET/CT.

[g] Correlative Research Studies: Blood and urine sample as described in section **4.1**.

[h] Filling out of the advance directive will be offered, but obtaining of it is not required. For details see Section **9.3**

3.4 SURGICAL MANAGEMENT

After their initial on-study evaluation, patients will be staged according to findings on imaging studies with respect to primary tumor site, size and metastases. Surgical resection of NET and/or medical managements will be recommended based on standard practice guidelines [58].

Surgery will be recommended to manage lesions within the gastrointestinal tract and pancreas under the following circumstances:

3.4.1 Patients with solid lesions that are thought to be NETs by non-invasive imaging studies will be considered for surgery if:

- Their solid lesion is enlarging on serial imaging studies.
- Their solid lesion is associated with symptoms consistent with gastrointestinal or pancreatic NET.
- A solid lesion in the head of the pancreas is ≥ 2 cm in size.
- A solid lesion in the body or tail of the pancreas is ≥ 3 cm in size.
- Gastrointestinal functional tumors will be treated according to standard clinical practice.
- Metastases will be addressed according to standard clinical practice.

3.4.2 Patients who present with evidence of cardiac risk factors will undergo a cardiac evaluation prior to surgical intervention according to standard clinical practice.

3.4.3 In patients who require an operation and have ^{68}Ga-DOTATATE uptake on PET/CT, a radio-guided surgery will be performed using a hand-held gamma probe. These patients will get a ^{68}Ga-DOTATATE injected 1.5 to 2 hours before the time of the operation. A dose of 5 mCI of ^{68}Ga-DOTATATE will be injected. During the surgical procedure, lesions will be localized using the gamma probe with comparison of target lesion activity to non-target tissue activity as uptake of ^{68}Ga-DOTATATE in normal tissues could be variable.

For patients undergoing surgical resection, tissue that is removed will be analyzed in the Surgical Pathology Department to confirm diagnosis, and with the patient's consent, a small part of the resected tissue will be used for research purposes (as described in section **1.1** and section **4.1**). After procurement for the Surgical Pathology Department, we will collect at least 0.5x0.5x0.5 cm of tissue sample that remains.

3.5 STANDARDIZED ^{68}GA-DOTATATE PROTOCOL

Fasting is not required prior to the imaging study. An IV line with a large bore (21 gauge or more) will be placed preferably in the antecubital vein, and, with the patient supine, around 5mCi of the ^{68}Ga-DOTATATE will be administered intravenously, followed by incubation for approximately 60 minutes. Then the patient will be positioned in a PET/CT scanner and images from the upper thighs to the base of the skull will be obtained. In patients with tumor induced osteomalacia, images from the top of the head to the toes will be obtained.

To date, there are no known allergic reactions to ^{68}Ga-DOTATATE.

3.6 SUPPORTIVE CARE

Supportive care will be provided to the patients by the Endocrine Oncology Branch as is indicated by either their admission work-up needs or by their postoperative management after a surgical procedure to manage the lesions.
Medical management of the symptoms related to the patient's disease may be provided by the patient's referring physician.

In the event that a subject has a reaction (allergic) to the radiotracer, all appropriate medical measures will be taken immediately. In rare instances, this may entail admission to the hospital for observation.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.7.1 Off-Study Criteria

- Discretion of the Investigator^{+}.
- Patient or parent/guardian requests to be taken off study
- Patient non-compliance with protocol appointments or imaging studies^{+}
- A serious or intolerable adverse event related to the study drug occurs^{+}
- Patient may not be taken off study until intolerable adverse event has stabilized or resolved^{+}.
- Patient has completed 5 year follow up period^{+}.
- Positive pregnancy test^{+}
- Lost to follow up
- PI decision to close the study
- Death

+ Subjects under the age of 18 should not be removed from study for these reasons as it is required that they give informed consent for the ongoing use of their specimens and data once they have reached the age of majority.

3.7.2 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 BIOSPECIMEN COLLECTION

4.1 CORRELATIVE STUDIES FOR RESEARCH

The differentiation status (Grade 1/2/3) of the tumor lesions on pathology will be correlated with imaging findings from ^{68}Gallium-DOTATATE PET/CT and with disease progression, extent of disease (Stage) and clinical outcome. This will determine the predictive value of ^{68}Gallium-DOTATATE imaging and will provide information on the severity of disease. Pathology of the NETs will be staged according to the WHO classification for NET 2010 [14].

We will analyze somatostatin receptor expression levels and subtypes in tumor samples from patients who undergo surgical intervention by immunohistochemistry and Western blot for protein expression [49] and with quantitative RT-PCR for mRNA expression. This will be compared to ^{68}Gallium-DOTATATE uptake in the same lesion [50]. With this information on actual receptor status of the lesions, future feasibility of radiolabeled somatostatin treatment for metastatic NET ("peptide receptor radionuclide therapy") could be evaluated.

Additionally, we will collect a blood sample (Red/yellow SST tube with Gel and Clot Activator additive, 2x8ml tubes for a total of 16ml) and urine sample (1 container of maximum 100mL) at baseline for each patient, in order to perform proteomics for the discovery and validation of biomarkers.

4.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

In patients who undergo surgical treatment, the samples will be immediately snap frozen in liquid nitrogen and transported to the Endocrine Oncology Lab by calling 301-435-7891. Samples will be labeled with the date and time of acquisition, the type of tissue and patient study ID. Upon receipt in the lab, samples will be bar coded and logged in to the tissue database, LabMatrix. Tissue will be stored in -20°C or -80°C freezers until molecular analysis. All freezers are monitored and are on separate emergency generator lines.

In all patients, 2 research blood tubes and a urine sample will be collected at baseline, collected at the phlebotomy station for outpatients or at our inpatient units. They will be immediately kept on ice and transported to the Endocrine Oncology Lab by calling 301-435-7891.
Samples will be labeled with the date and time of acquisition, the type of sample and patient study ID. Upon receipt in the lab, samples will be bar coded and logged in to the tissue database, LabMatrix. Tissue will be stored in -20°C or -80°C freezers until analysis.

- All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss.
- If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

- The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

5.1.1 Clinical Data

Clinical data including summary and demographic data will be collected and entered into NCI CCR Database, LabMatrix. Adverse events occurring during any scanning session will be recorded. Adverse events which are designated possibly, probably or definitely related to ^{68}Gallium-DOTATATE PET/CT scans will also be recorded.

If patients require surgery, data from preoperative and postoperative course and unanticipated problems will be collected. Tumors visualized on imaging studies will be measured using tridimensional tumor measurements (or other appropriate units of measure) at baseline and at each follow up visit.

Patients will undergo monitoring of their disease, operative intervention when indicated, and follow up as per standard of care. Patients who meet the standard of care criteria for resection of their disease will undergo an operative procedure and may receive extensive care in the ICU. The principal investigator or designee will closely monitor and document the clinical care and treatment of each patient as per standard of care at the NIH Clinical Center. As per NIH Clinical Center standards of practice, the Occurrence Reporting System will be used to report any clinical events meeting these reporting criteria.

Only events that meet the definition of an unanticipated problem or a grade 5 event will be recorded if the event occurs as a result of standard treatments that patients may receive on this protocol.

Imaging data will include storage of the reconstructed images and image derived parameters on a secure, password protected lab imaging database. Images may also be stored in the clinical center PACS. The lab imaging database will be stored and maintained in the CC PET department facilities. Personal identifiers will not be used when storing data.

5.1.2 Safety Data

The following safety data will be collected and evaluated according to the Study Calendar (Section **3.3**):

- Data to confirm eligibility
- Clinical laboratory variables: serum biochemistry and hematology
- Vital signs: systolic and diastolic BP, heart rate, body temperature, and respiration rate
- Physical examination, signs and symptoms
- AEs

SAEs will be recorded if they occurred as follows:

- After a subject first received ^{68}Gallium-DOTATATE and throughout the subject's follow-up period,
- During the subject's follow up period, and for which a causal relationship to ^{68}Gallium-DOTATATE cannot be ruled out.

Interpretation and follow-up of abnormal results will be done on a case by case basis in conjunction with the individual clinical situation. Any clinically significant abnormal finding, or change in one that represents a worsening from baseline, is an AE. Once a decision is reached to report a finding as an AE, the investigator is required to follow the procedure described for AE notification.

5.1.3 Imaging Data

Extracted imaging data include:

(1) PET imaging data will include maximal standardized uptake values (SUV) for each region of interest, correlation with the CT images of the PET/CT and, when feasible, with the IV contrast CT.

(2) All image data will be stored on a secure server, with access limited to credentialed users. This will permit flexible numeric raw data extraction for quantitative analysis and creation of summary data reports.

5.1.4 In-111-OctreoScan Studies

In the original version of this protocol and Amendments A-G (implemented between September 2013 and July 2015) involved obtaining both Ga-68-DOTATATE PET CT studies and In-111-OctreoScan Studies, considered then to represent the "gold standard" in somatostatin receptor imaging. The primary objective of the original protocol was to evaluate the accuracy of Ga-68-DOTATATE PET/CT in detecting neuroendocrine tumors. For this, Ga-68-DOTATATE scans

were compared with In-111OctreoScans. Once the superiority of Ga-68-DOTATATE PET/CT was proven, the use of In-111OctreoScan was abandoned.

Our intention is now to reanalyze these tandem scans and their comparison from a different perspective. This new concept "theranostics". Theranostics combines the diagnostic agent, in this case Ga-68-DOTATATE, with its therapeutic counterpart, in this case Lu-177-DOTATATE. While Ga-68 is a positron emitter and therefore used for imaging and diagnosis of neuroendocrine tumors, Lu-177 is a beta minus emitter used for treatment of these tumors through local radiation. Both radioisotopes are bound to the same molecule, i.e. DOTATATE, ensuring that we treat tumors which we have clearly demonstrated to exist and which bear the somatostatin receptors targeted by the treatment agent.

A seminal article was published in the NEJM in Jan. 2017 communicating encouraging results of a phase 3 trial using Lu-177-DOTATATE for treatment of midgut neuroendocrine tumors [59]. The selection of the patients was based on SSTR positive tumors detected on In-111OctreoScan, at that time the only approved agent for SSTR imaging. As Ga-68-DOTATATE became an FDA approved agent and is recognized as superior to In-111OctreoScan, we have no doubt that Ga-68-DOTATATE will substitute In-111OctreoScan in determining the eligibility for Lu-177 DOTATATE treatment. Lu-177 DOTATATE is currently being evaluated by the FDA and is anticipated to be approved. Our comparison between the findings on the two scans, will aim at translating the criteria used for the In-111OctreoScan in establishing eligibility for Lu-177-DOTATATE treatment into emerging criteria for Ga-68-DOTATATE. This blinded retrospective review of the scans is considered of particular value and applicability as the approval for the treatment agent (Lutathera) is anticipated by early next year with the Ga-DOTATATE being already widely available.

Practically we will compare 219 tandem scans done between Oct. 2013 and July 2015. The images will be reviewed to determine number and localization of the lesions on each scan together with their intensity of uptake based on Krenning score on OctreoScan, and Krenning score and SUV max on 68Ga-DOTATATE. The Krenning score classifies lesion uptake as follows: 0=no uptake; 1: uptake<liver; 2: uptake =liver; 3: uptake> liver; 4: uptake > spleen/or kidney. Target lesions will be decided based on highest intensity of uptake on each scan. Only lesions present on both scans will be compared. All tracer avid lesions will be considered positive. No additional imaging studies will be used to assess their true positive status.

The purpose of this project is to reevaluate the criteria used for establishing eligibility for PRRT based on planar OctreoScan in the Netter1 trial, and develop updated ones adapted to the current reality of clinical practice using Ga-68-DOTATATE for imaging of neuroendocrine tumors. Access to PRRT is crucial to many NET patients with metastatic or unresectable disease for which not many good treatment options are otherwise available. Both patients and physicians caring for NET patients will benefit from a valuable tool guiding their decision for PRRT versus other treatment options. The Society for Nuclear Medicine and Molecular Imaging (SNMMI) has endored our initiative.

The group of radiologists to undertake this task will be composed of three experts, members of the SNMMI (Society of Nuclear medicine and Molecular Imaging) and part of the Ga-68 user group. The radiologists are:

- Corina Millo, MD, staff clinician in the PET Department, CC, NIH, an AI on the protocol.
- Thomas Hope, MD, Radiology Department, UCSF.

  4150 Clement St, San Francisco CA 94121

  415-221-4810, thomas.hope@ucsf.edu
- Jeremie Calais, MD, Molecular and Medical Pharmacology Department, UCLA

  UCLA Mol & Med Pharmacol, BOX 956948, AR 237A CHS, Los Angeles,

  CA 90095-6948

  310-825-3617, j.calais@mednet.ucla.edu

This project requires data transfer to the outside readers using de-identified DICOM images files. These will be transferred via a commercial file sharing service or by the NIH Secure File transfer (https://emib.cit.nih.gov/services/Pages/secureFilestransfer.aspx).

The data will be de-identified prior to transfer with none of the 3 readers having access to patient identifiers.

Prior to release of de-identified data, an MTAs will be executed with each extramural investigator listed above.

5.2 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

6 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

6.1 DEFINITIONS

6.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant requiring treatment. For this study, AEs will include events reported by the patient, as well as new onset abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or laboratory abnormality outside the range of normal limits or greater than 50% increase from baseline value if the baseline is above the upper limit of normal or worsening of a pre-existing condition or abnormality is considered an AE.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. AEs should be reported up to 30 days following the last dose of study drug. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **6.2** and **6.3**.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

6.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means 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.

6.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

6.1.5 Serious Adverse Event

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

- Death.

- A life-threatening adverse drug experience.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

6.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

6.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol.

6.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

6.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.2 NCI-IRB AND CLINICAL DIRECTOR (CD) REPORTING

6.2.1 NCI-IRB and NCI CD Expedited Reporting of, Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

6.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

    NOTE: Grade 1 events are not required to be reported.

6.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

6.3 IND SPONSOR REPORTING CRITERIA

6.3.1 Expedited Adverse Event Reporting Criteria to the IND Sponsor

An investigator must immediately report to the sponsor using the mandatory MedWatch form 3500a, any serious adverse event whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between

the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

Events will be submitted to:

NIH Clinical Center – PET Imaging Department
Attn: Peter Herscovitch, MD
10 Center Drive Rom 1C495
Bethesda, MD 20892-1180
Telephone: 301-451-4248
pherscovitch@nih.gov

6.3.2 Expedited Adverse Event Reporting Criteria to the IND Manufacturer

Investigators will submit reports of all SAEs, regardless of attribution to RPS within 24 hours of learning of the events. For initial SAE reports, Investigators should record all case details that can be gathered within 24 hours on a SAE Report Form and submit the report via fax to:

Research Pharmaceutical Services (RPS) Drug Safety

Fax Number: (800) 516-5542 or (+ 1) 484 533-2817

Relevant follow-up information should be submitted to RPS's Drug Safety Department as soon as it becomes available and/or upon request.

6.4 Data and Safety Monitoring Plan

6.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively enrolled on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

6.4.2 Sponsor Monitoring Plan

Due to the "Low Risk" categorization of observational studies that use PET IND Radiopharmaceuticals, an annual monitoring of the clinical investigation will be conducted by completing the worksheet found in section **11.3**, Appendix C. The monitoring worksheet may be completed at the time of Continuing Review by the Principal Investigator or a designee (designee must be familiar with the study. Completed worksheet must be signed by the PI.

7 STATISTICAL CONSIDERATIONS

The primary objective of this prospective study is to assess the diagnostic accuracy of the new imaging technique ^{68}Gallium-DOTATATE PET/CT scan for patients with NETs. Based on the existing literature, the rate of correct classification of this new imaging technique against the gold standard of Octreoscan SPECT is about 85% [46, 60]. Assuming that on average 2 lesions will be evaluated for each patient, and that classifications of the multiple lesions from the same patient is modestly correlated with a correlation coefficient set at 0.2, the sample size is determined to achieve a desired precision of the estimate of the proportion of correct classification measured by the width of the 95% confidence interval. A few scenarios of sample size and true rate of correct classification are considered and listed in the following table.

Number of patients	True proportion of correct classification	95% confidence interval
50	0.85	(0.77,0.93)
100	0.85	(0.80,0.90)
150	0.85	(0.81, 0.89)
200	0.85	(0.81,0.89)
50	0.87	(0.80,0.94)
100	0.87	(0.82,0.92)
150	0.87	(0.83,0.91)
200	0.87	(0.83,0.91)

If the true proportion of correct classification is 0.85, with 50 patients, the 95% expected confidence interval is (0.77, 0.93), and with 100 patients, the 95% expected confidence interval is smaller (0.80, 0.90). The confidence interval is shortened only slightly even if the sample size is doubled to 200. This is also the case when the true proportion of correct classification is 0.87. Even though there does not appear to be a big difference in the confidence interval for the estimated accuracy of ^{68}Ga-DOTATATE for the sample size of 50 patients as compared to 100 patients, based on the literature [61], less than 20% of the patients are expected to have negative NETs. As a result, with the total sample size of 50 patients, likely less than 10 patients would have negative NETs, which is too small to estimate the specificity with precision. Hence the study is targeted at a sample size of 100 patients resulting in a 10% width of the 95% expected confidence interval for the estimate of the correct classification rate of ^{68}Ga-DOTATATE. As such, the study has an adequate size to estimate both the correct classification rate and sensitivity and specificity.

Studies have shown specificities for ^{68}Ga-DOTATATE PET/CT as high as 90% for primary and metastatic NETs [42, 60]. Patients included in the protocol will have yearly follow-up with

conventional imaging studies for assessment of changes in lesions which would minimize false positives. Furthermore, in patients who require surgery, diagnosis will be confirmed by histopathology.

Based on current protocols for MEN1 and VHL and patients seen by provider on these protocols, we estimate an accrual rate of 3-10 patients per month. This includes patients with VHL and pancreatic NETs and patients with MEN1. Currently the VHL protocol includes up to 220 patients followed every year, with an accrual rate of 4 new patients on average per month [range 2-7/month in 2012]. For patients with MEN1 patients, up to 200 patients are followed on a current protocol. If we assume that 50% of those patients are willing to participate and adding the new patients recruited from outside the NIH and sporadic cases, we should reach an accrual rate between 3-10 patients per month. Hence, the total length of accrual period for this study is estimated to be 10 months to 3 years.

One of the secondary objectives of the study is to determine whether DOTATATE uptake value predicts tumor and disease progression. To study this, the SUV uptake of ^{68}Ga-DOTATATE on PET imaging will be compared between patients who require operative intervention and those who do not, and SUV uptake will be correlated to tumor size and growth rate of the tumors. Among patients with sporadic or familial gastrointestinal and pancreatic NET to be accrued into this study, it is expected that 10-30% of them will require operative intervention. With a targeted total of 100 patients: approximately 20 requiring operative intervention and 80 not requiring operative intervention. The study would have 84% power to detect a standardized mean difference (mean difference/SD) of 0.75 in SUV uptake of ^{68}Ga-DOTATATE between the two groups of patients, using the two-sample t-test at the 5% significance level. Two recent published studies [46, 62] show that the variability of SUV uptake of ^{68}Ga-DOTATATE is large, and the standard deviation is comparable to the mean value. If the variability of SUV uptake of ^{68}Ga-DOTATATE of the current study is comparable to that in those previous 2 studies, then detecting a standardized mean difference of 0.7 would be close to detecting a 1.75 mean fold change.

Additionally, radio-guided surgery using a gamma probe will be used for patients that require an operation and have lesions confirmed to have positive uptake on ^{68}Ga-DOTATATE PET/CT. The main goal is to assess feasibility of this new technique with radio-guided surgery as this approach may facilitate the intra-operative detection of some NETs or detect additional lesions. For measurements of the uptake by the probe, the count rate signal will be used as well as the ratio between the target and the background (normal tissue). Further, the sensitivity of radio-guided surgery will be compared to pre-operative ^{68}Ga-DOTATATE PET/CT SUV uptake and to surgical palpation for intra-operative detection of NETs. The number of lesions and their SUVs detected on PET/CT, the number detected by the gamma probe and by visualization and surgical palpation will be compared. The final histological diagnosis will be used as the gold standard for correct identification of NETs.

Another important secondary objective of the study is to determine the relationship between somatostatin receptor status (SSRT) in tumor samples and ^{68}Gallium-DOTATATE uptake. Based on the existing literature [49, 63], SSTR score is approximately uniformly distributed. With 20 expected patients requiring operative intervention, the study will have 82% power to detect a standardized mean difference of 1.2 between half of the patients with low SSRT-2 scores (0-1) versus the remaining patients with high SSTR-2 scores (2-3) using the two-sample t-test at the 10% significance level. The power would be less than 80% if the standard mean difference is

less than one. The relationship between subtypes of SSRT and ^{68}Gallium-DOTATATE uptake will also be examined, but it is expected that they have lower affinity to ^{68}Gallium-DOTATATE uptake than SSRT-2. As a secondary objective, the outcome will be useful in generating hypothesis and planning for future studies.

7.1 AMENDMENT D

We will increase our accrual ceiling for several reasons. The initial sample size calculation was based on a non-inferiority analysis of ^{68}Gallium-DOTATATE PET/CT to octreoscan SPECT, the currently used imaging study to detect NETs. Our interim analysis in 50 patients shows that ^{68}Gallium-DOTATATE PET/CT is much more accurate than Octreoscan SPECT (overall accuracy of 78% for ^{68}Gallium-DOTATATE PET/CT; 60% for Octreoscan SPECT, 74% for triphasic CT scan% in a per patient analysis). Thus, the sample size calculation has been revised to determine if ^{68}Gallium-DOTATATE PET/CT is more accurate than CT scan. Based on the data collected, the difference in the diagnostic accuracy between these two imaging techniques is 4% and the proportion of discordant imaging results is 12%. In order to detect 5% difference between these two imaging techniques with 80% power and with 10% discordant rate, 295 patients are required. The comparison is based on McNemar's chi-squared test at the 5% significance level. Thus, we are increasing our accrual ceiling to 295 patients. In addition, in a per lesion analysis between the two imaging techniques (^{68}Gallium-DOTATATE PET/CT and triphasic CT), there were discordant results in 30 of the 50 subjects (in 26 patients, ^{68}Gallium-DOTATATE PET/CT found additional lesions, in 4 patients CT found additional lesions, 20 patients had concordant (positive or negative) results). Additional reasons to increase the accrual ceiling are: 1) the most accurate way to confirm the results and findings from ^{68}Gallium-DOTATATE PET/CT scan is to compare them to pathologic evaluation of resected tumors. Thus far, 21 of 84 subjects have been recommended to have surgical treatment because of metastatic disease detection on ^{68}Gallium-DOTATATE PET/CT, and 9 patients have had a surgical procedure with pathology confirming the results (all true positives). Therefore, in order to increase the power of this comparison, an increase in accrual would be necessary. 2) We have used a gamma probe for intra-operative detection of NETs, in two subjects the results were positive and in order to validate this technique, an increase in number of patients would be needed.

7.2 AMENDMENT H

The sub-aim of Aim 1 was to determine the accuracy of ^{68}Ga-DOTATATE to detect unknown primary NETs. However, the current study is under-powered to achieve the first aim in detecting a 20% difference in detection rate between the two imaging modalities (^{68}Ga-DOTATATE and CT scan). Of 290 patients accrued to the study, as of amendment G, twenty-one had unknown primary NETs. Under the current accrual trend, assuming a total of 25 patients in the entire cohort have unknown primary 40% of whom were identified by ^{68}Ga-DOTATATE. Assuming the proportion of discordant imaging result is 24%. The current study would have only 50% power to detect a 20% difference using McNemar's chi-squared test at the 5% significance level. In order to achieve 90% power, the number of patients with unknown primary NETs need be increased to 55 subjects total (34 excluding those already enrolled).

To date, 24 patients accrued in the current study, as of amendment G, underwent radio-guided surgery with a total of 56 lesions detected on histology. Based on the preliminary data, lesion-

based detection rate of DOTATATE gamma probe and CT scan/operative visualization was 71% and 57%, respectively. Assume on average 2 lesions per patient are identified by histology. The variance of the difference in detection rate between the two imaging guided procedures is given by

$$Var(\hat{P}_1 - \hat{P}_2) = n^{-1}(V_1 + V_2)[1 + (k-1)r_1] - 2n^{-1}r_2\sqrt{V_1 V_2}$$
$$= \frac{\sigma^2}{n}$$

, where $V_i = \frac{P_i(1-P_i)}{k}$, P_i= true detection rate(i=1 for DOTATATE gamma probe and i=2 for CT scan), $\hat{P}_i$= estimated detection rate , k= number of lesions per patient on average, r_1= inter-lesion correlation, r_2= intra-lesion correlation between the , and n= number of patients. Based on prior studies, inter-lesion correlation arising from multiple lesions of the same patient is set at 0.2 and intra-lesion correlation between DOTATATE and CT is set at 0.5. With these values and assuming P1=0.72 and P2=0.57, σ=0.40. To achieve 90% power in detecting 15% difference in detection rate between the two imaging modalities, with σ=0.40 a total of 85 patients (including the 24 patients already enrolled) are required using a two-sided Z-test at the 5% significance level.

Therefore, we are increasing our accrual ceiling to 390 patients.

7.3 DETAILED ANALYSIS

We recently performed an analysis of the detection rate of the 3 imaging modalities in the first 131 patients enrolled in the study for known or suspected gastrointestinal and pancreatic neuroendocrine tumors. Lesions detected on any of the 3 imaging modalities were defined as the denominator. ^{68}Gallium-DOTATATE detected 95.1% of lesions compared to Octreoscan SPECT, which only detected 30.9% of lesions ($p<0.0001$). Furthermore, in four out of 14 patients, ^{68}Gallium-DOTATATE PET/CT found a previously unknown primary tumor not detected by Octreoscan SPECT. Twenty-five patients underwent surgical resection for their primary tumors and/or metastases. An analysis of imaging concordance with histopathology showed that ^{68}Gallium-DOTATATE PET/CT found true-positive lesions 63.7% (72 out of 113 lesions) compared to 22.1% (25 out of 113 lesions) for Octreoscan. In assessing the impact of ^{68}Gallium-DOTATATE PET/CT on clinical management, ^{68}Gallium-DOTATATE PET/CT detected additional lesions in 93 out of the 131 patients (71.0%) compared to Octreoscan SPECT. Forty-four out of the 93 patients with additional lesions were found to have metastatic disease. These additional findings led to a change in management in 43 out of the 131 (32.8%) of patients. Given the clear imaging superiority of ^{68}Gallium-DOTATATE PET/CT to Octreoscan, we will no longer perform Octreoscan in patients being enrolled and will compare its accuracy to CT/MRI scanning. This will result in lower radiation exposure to subjects and reduced cost.

8 COLLABORATIVE AGREEMENTS

There are MTA agreements under negotiation for the study referenced in section 5.1.4 with:

UCSF (pending)

UCLA (pending)

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

Patients with suspicious neuroendocrine lesions, unknown primary tumor or metastatic gastrointestinal or pancreatic neuroendocrine disease found on anatomic imaging (CT/MRI) or patients with biochemically active disease will be selected for this study. Both functional and non-functional solid tumors will be included in this study. Furthermore, asymptomatic and symptomatic, and both sporadic and familial cases of NETs (such as VHL, MEN1) will be included who have biochemical or anatomic imaging evidence of disease. Patient selection for this protocol will not be based on gender, race or ethnic background.

9.2 PARTICIPATION OF CHILDREN

Children below the age of 10 will not be included on this protocol. Only patient age 10 and older will be eligible for this study because no dosing or adverse event data are currently available on the use of ^{68}Gallium DOTATATE in patients younger than 10 years of age. Therefore, children under 10 are excluded from this study.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

In cases where the patient is unable to give informed consent, an appropriate surrogate, such as a DPA, will be identified as per the NIH Clinical Center (CC) MAS M87-4 policy. In that case, members of the protocol team will describe the protocol, alternative therapies, and the risks and benefits of each to the patient's DPA for health care and the DPA may give informed consent on behalf of the patient. If possible, signed assent will be obtained from patients unable to give informed consent. For NIH CC patients, the assent signature line at the end of NIH form 2514-1 will document such assent. As patients may be cognitively impaired due to brain metastases, and a DPA is being used because the patient is unable to understand the consequences of their assent or dissent, the Study PI has determined that the designated DPA should be allowed to make the decision for the patient to enroll in this protocol. In cases where the patient's DPA is unable to be present in person at the Clinical Center, obtaining informed consent via technology and/or electronic processes is permissible. In these cases, the informed consent discussion will be carried out over telephone and giving of informed consent may be done by phone, fax or email. The informed consent process will be documented in the patient's medical record and on the informed consent document. This process will be performed by the local Principal Investigator or designee.

Re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of benefit from research participation (section **9.4**), all subjects $\geq$18 years old will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIHMEC Policy 87-4 for appointing a surrogate decision maker for adult subjects

who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 Evaluation of Benefits and Risks/Discomforts

There is no direct benefit for patients participating in this study but if the study results show ^{68}Gallium-DOTATATE PET/CT imaging to be more accurate, the future application of this imaging modality in other patients could lead to early detection of solid gastrointestinal or pancreatic lesions and early management of these lesions, which may have an impact on the overall course of the disease. This study also offers the benefit of surgery, when patients meet the criteria for resection, in an institution with vast experience with patients who have NETs.

Risks and discomforts of the experimental procedure are expected to be low and related to the risks of ^{68}Gallium-DOTATATE, and SPECT/CT imaging. Most complications are expected to be minor and require no treatment.

Risks and discomforts associated with ^{68}Gallium-DOTATATE PET/CT imaging are discomfort of an IV placement and the theoretical effects of the amount of additional radiation exposure. The effective dose for adults per PET/CT scan with 5.0 mCi of ^{68}Ga-DOTATATE administered activity is 1.1 rem per year or 1.6 rem if receiving two ^{68}Ga-DOTATATE injection of 5.0 mCi of ^{68}Ga-DOTATATE in case of surgery, which in both cases is below the maximum of 5.0 rem per year recommended by the radiology safety guidelines for adult research subjects. The effective dose for children over 15 per PET/CT scan with 5.0 mCi of ^{68}Ga-DOTATATE administered activity is 0.30 rem per year or 0.40 rem if receiving two ^{68}Ga-DOTATATE injection of 5.0 mCi of ^{68}Ga-DOTATATE in case of surgery, which in both cases is below the maximum of 5.0 rem per year recommended by the radiology safety guidelines for adult research subjects. The effective dose for children between 10 and 14 per PET/CT scan with 5.0 mCi of ^{68}Ga-DOTATATE administered activity is 0.35 rem per year or 0.45 rem if receiving two ^{68}Ga-DOTATATE injection of 5.0 mCi of ^{68}Ga-DOTATATE in case of surgery, which in both cases is below the maximum of 5.0 rem per year for adult research subjects and 0.5 rem per year for children research subjects recommended by the radiology safety guidelines for adult research subjects. In this study, the subject will be required to lie still on his back for around 30 minutes during image acquisition in the PET/CT scanner, and this might produce some discomfort.

Risks associated with the surgical procedures to manage lesions in the pancreas will vary based on the type of lesion and the planned surgical procedure and are part of standard clinical care. These risks will be discussed in depth on a patient-by-patient basis.

9.5 Risks/Benefits Analysis

The risks of participation are low based on the small cold and radioactive doses used and prior knowledge of a low rate of AEs for ^{68}Gallium-DOTATATE. For patients who have solid tumors that are not currently amenable to surgical resection, the risk of blood drawing and non-invasive imaging is minor. This study also offers the benefit of surgery, when patients meet the criteria for resection, in an institution with vast experience with the patient with NETs.

9.6 Consent and Assent Process and Documentation

All patients and/or the patient's parents or legal guardian (if he/she is < 18 years of age) who are being considered for this trial will undergo informed consent prior to being enrolled on the trial.

The PI or associate investigator will perform the consenting process. Patients and family members when applicable will be asked to read the consent and will be encouraged to ask questions. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. Patients will be enrolled after the consent document has been signed. Separate consents will be obtained for any surgical procedures performed.

9.6.1 Telephone Re- Consent Procedure

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail to the subject.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.6.2 Informed consent of non-English speaking subjects

We anticipate the enrollment of Spanish speaking research participants into our study. The IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2.

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2), 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

9.6.3 Consent of Children

The investigators are requesting a waiver from the IRB to allow only one parent to sign the informed consent to enter a child on the protocol. Because many patients must travel to the NIH

from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. When guardianship status of the child is uncertain, documentation of custody status must be obtained. In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained by telephone via the procedure described in section **8.5.1**.

The PI or an associate investigator on the trial will obtain consent. Where deemed appropriate by the clinician and the child's parents or guardian, the child will also be included in all discussions about the trial and verbal assent will be obtained. The parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent.

All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

9.6.4 Verbal Assent of Children

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Written assent will not be obtained from children as the study holds out the prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of the research. Verbal assent will be obtained and the parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

9.6.5 Re-Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require re-consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. Given the length of time that has transpired for some of the subjects since their last visit for this study, we request waiver of informed consent for those individuals who have completed their participation in the research study.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
    a. Retention of these samples or data does not affect the welfare of subjects.
(3) The research could not practicably be carried out without the waiver or alteration.
    a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate

them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

a. We only plan to request a waiver of reconsent for those subjects who have been lost to follow-up or who, prior to the approval of Amendment J, have been taken off study prior to reaching the age of majority.

10 PHARMACEUTICAL INFORMATION

10.1 DOTATATE (IND 119098)

10.1.1 Source

^{68}Ga-DOTATATE will be manufactured and tested at the Positron Emission Tomography (PET) Department located at the Warren Grant Magnuson Clinical Center (CC) of the National Institutes of Health (NIH), 10 Center Drive (Building 10, Room 1C401) Bethesda Maryland. The Investigational Drug will be sponsored by the PET Department at NIH. Dr. Peter Herscovitch is the primary contact.

Similar to the ordering procedures of all traces available from the PET department, ^{68}Ga-DOTATATE can be ordered via CRIS (physicians order for the dose).

10.1.2 Toxicity

Data from several preliminary studies in human provides strong evidence that the amount of investigational DOTATATE in mass quantity and the amount of radiation are acceptable in terms of risk (Reference: ^{68}Gallium-DOTATATE IND 111,972 sponsored by Vanderbilt University).

Additionally, as reported by Virgolini et al. [64], the EANM's procedural guidelines for PET/CT tumor Imaging with ^{68}Ga-DOTA-Conjugate peptides (including DOTA-TATE) indicates that within the administered activity range around 185 MBq (recommended activity for good image quality estimated to be at least 100MBq) injection of less than 50µg cold mass is not expected to have any clinically significant pharmacological effects. Precautions to be taken into considerations for clinical use of ^{68}Ga-DOTATATE include pregnant females with suspected or confirmed pregnancy, or breastfeeding. Additionally administration of subjects under 18 years of age should also be carefully evaluated.

As reported by Walker et al. [65] in a recent publication in JNM "First report of Measured human dosimetry with ^{68}Ga-DOTATATE" dosimetry data collected at two or three time points (30, 60, and 90 minutes after IV injection with an average of 5 mCi in 6 patients) injected with [68Ga]DOTA-TATE, concluded that the radiation dosimetry from ^{68}Ga-DOTATATE is similar to and slightly less in total effective dose to the very popular and highly used Radiopharmaceutical 18F-FDG.

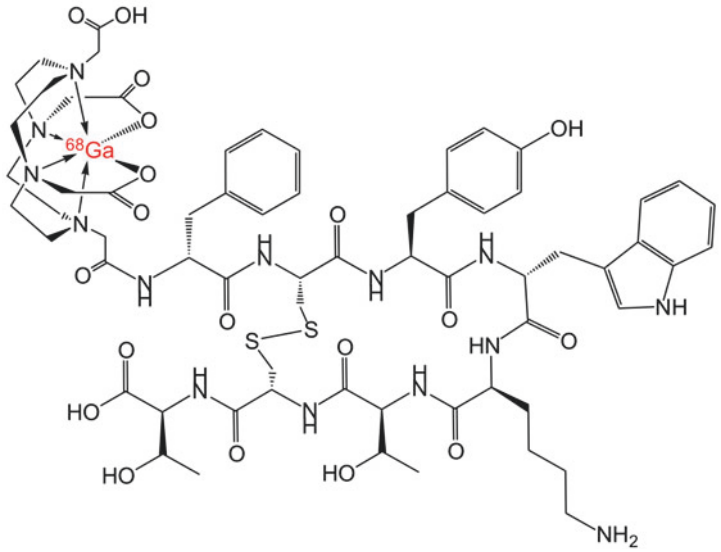
10.1.3 Formulation and preparation

10.1.3.1 Formulation

[^{68}Ga]DOTA-TATE DRUG PRODUCT COMPONENTS

Component	Composition/batch
Drug Substance [^{68}Ga]DOTA-TATE (Substrate Starting Material: 50 µg ±1 µg of DOTA-(Tyr3)-Octreotate)	**5 - 50 mCi @ EOS** (End of synthesis calibration time)
Other ingredient(s) 1. 0.9% Sodium Chloride Injection, USP 2. Ethanol, USP 3. Sterile Water for Injection, USP	 13.0 mL 1.0 mL 1.0 mL

- Name: Gallium-DOTA-(Tyr3)-octreotide(68Ga) injection
- Formula of DOTATATE: C65H90N14O19S2
- Formula Weight: 1489.35
- Half-life: approximately 68 min
- Radiochemical Purity: >90% (HPLC)
- pH: Range 4.0-8.0 (typically at pH 5)
- Appearance: clear and colorless solution
- Structure:



- Mechanism of Action:

DOTA-TATE is an amide of the acid DOTA which acts as a chelator for a radionuclide, and

(Tyr3)-octreotate, a derivative of octreotide. The latter binds to somatostatin receptors, which are found on the cell surfaces of a number of neuroendocrine tumors, and thus directs the radioactivity into the tumor.

The primary indication of [^{68}Ga]DOTA-Conjugate peptides PET/CT is the imaging of NETs. [^{68}Ga]DOTATATE (DPhe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr), an analogue in the hydroxy group at the C terminus is changed to a free carboxylic group. This results in further increased binding affinity, internalization rates and selectivity for SSRT [66].

10.1.3.2 Preparation

Each batch of [^{68}Ga]DOTA-TATE injection will be produced in a single vial. The drug is composed of a small amount of 0.9% Sodium Chloride Injection, USP (13mL), Ethanol, USP (1mL), Sterile Water for Injection, USP (1mL). The drug solution will be manufactured sterile and free of pyrogens for intravenous injection.

The final preparations of the agent to reach the specific prescribed administration dosage (in mCi) will be conducted by the PET Radiopharmacist.

Before final release of the [^{68}Ga]DOTA-TATE injection for administration, all specifications listed in the FDA approved IND application will be verified.

10.1.4 Stability and Storage

[^{68}Ga]DOTA-TATE injection will be stored at controlled room temperature, with an expiration date of 2 hours from the End of Synthesis (EOS) calibration time.

10.1.5 Administration procedures

[^{68}Ga]DOTATATE will be administered intravenously in conjunction with the PET/CT scan. The one-time nominal injected dose will be 5 mCi in a volume of 3 - 5 ml containing up to 50 µg [^{68}Ga] DOTATATE.

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12 APPENDICES

12.1 APPENDIX A- DATA COLLECTION AT SCREEN/ENROLLMENT

Date of Visit:_____

Subject Data: Patient initials_____

1) Consent Signed: Date & Time_____

2) Physical Exam:

Height (cm or in)		**Weight (kg or lbs)**	
General: Vital Signs			
HR	**BP**	**RR**	**Temp**	**Pulse Ox**

Others	**Normal**	**If abnormal, please describe:**
HEENT		
Chest		
Cardiovascular		
Abdomen		
Integument		
Musculoskeletal		

Neurological		

3) Urine Pregnancy test required? (Please circle) Y / N

Results:_____ Date/Time: _____

4) Octreoscan available to all investigators? (Please circle) Y / N

Date of Octreoscan: _____

5) Laboratory Test

***Note: Please indicate below if following laboratory tests are performed:**

Date & Time of Laboratory Testing: _____

Test:	CBC (w/diff)	Comprehensive Metabolic Panel
Y / N		

6) Concomitant Medications:

Drug Name	Dose	Regimen	Indication	Date Initiated	Date Discontinued

7) Somatostatin therapy: Therapy name and dosage: _____

Regimen: _____
Date of Last dose: _____

Data Collection Completed by: _____ on _____

(Signature) (Date)

Printed Name:_____

12.2 APPENDIX B- DATA COLLECTION FOR FOLLOW-UP VISIT

Patient Initials _____ Patient Number_____

Date of visit: _____

Subject Data

Date & Time of Physical Exam/Vital Signs: _____

Height (cm or in)		Weight (kg or lbs)	
General: Vital Signs			
HR	BP (extremity)	RR	Temp	Pulse Ox

Others	Normal	If abnormal, please describe:
HEENT		
Chest		
Cardiovascular		
Abdomen		
Integument		
Musculoskeletal		
Neurological		

***Note: Please indicate below if following laboratory tests are performed:**

Date & Time of Laboratory Testing: _____

Tests	CBC w/diff	Comprehensive Metabolic Panel	AST	ALT	Bilirubin	BUN	Creatinine

Y / N							

AE Questionnaire Completed

1. **Have you had any new symptoms since the completion of your Gallium PET scan?**

   Yes____ No_____

2. **If yes, describe briefly.**

Signature _____ Date: _____

Printed Name:_____

12.3 APPENDIX C- CLINICAL INVESTIGATION MONITORING WORKSHEET

Clinical Investigation Monitoring Worksheet

For Protocols using PET IND Radiopharmaceuticals

NIH /CC/PET Department

The Food and Drug Administration (FDA) and the NIH Intramural Research Program require that the Positron Emission Tomography (PET) Department, NIH Clinical Center, ensures that every clinical research study performed using an IND it sponsors, has an adequate monitoring plan of the clinical investigation.

The Investigator can choose to follow their IC Guidelines/SOP to monitor the clinical investigation, or due to the "Low Risk" categorization of observational studies that use PET IND Radiopharmaceuticals, choose to conduct an annual monitoring of the clinical investigation by completing the following worksheet. The monitoring worksheet may be completed at the time of Continuing Review by the Principal Investigator or a designee (designee must be familiar with the study. Completed worksheet must be signed by the PI.

This worksheet is designed to assist investigators to conduct basic monitoring of their clinical investigation and identify areas where quality improvement may be needed. The key elements incorporated into this monitoring worksheet are protocol compliance, patient safety, and quality improvement.

Please complete, sign and return worksheet to the Tara Norouzi at the PET Department:
Tara Norouzi NIH/CC/PET
10 Center Drive, MSC1180 (Rm 1C-482) Bethesda, MD 20892
Phone: 301-435-8505 Fax: 301-480-5695 . norouzit@cc.nih.gov

Definitions	
AE	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
SAE	A serious adverse drug experience, resulting in death, life-threatening adverse drug experience, hospitalization, disability or congenital abnormality
Source Documents	Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated, x-rays, subject files)
CRFs	Case Report Forms are printed, optical, or electronic document(s) designed to record all of the protocol-required information. On-site monitoring should identify data entry errors (e.g., discrepancies between *Source Documents* and *CRFs)* and provide assurance that there are no missing data in source documents or CRFs
CAPA	Corrective And Preventive Action
Deviation	Any alteration/modification to the IRB-approved protocol
Site Signature and Delegation Log	A document that contains a list of all research staff involved in the conduct of the study, signatures, initials, delegated tasks and effective dates

GENERAL INFORMATION		
Protocol Number:		
Rad Auth Number (if available):		
Investigational Drug(s):		
IND Sponsor:	PET Department, NIH	
Protocol Title:		
Principal Investigator (PI):		
Reporting Period (covering this monitoring report)		
Date(s) Monitoring Conducted:		
Name of Monitoring Personnel:	Job Title:	Contact (Telephone):

MONITORING CRITERIA (Choose option A or B)	
Option A	☐ Annual Worksheet *(complete this monitoring worksheet)*
_____ Total No. of participating subjects in this reporting period _____ No. of subject files randomly chosen to be monitored by this worksheet (Monitoring of 10% of total No. of participating subject annually is recommended)	
STATEMENTS OF COMPLIANCE I understand and endorse the information in this clinical investigation monitoring worksheet. I agree to notify the IND sponsor if any of the information provided in this worksheet is amended. THIS WORKSHEET MUST BE SIGNED BY THE PRINCIPAL INVESTIGATOR	
Investigator's signature	
Date	
Option B	☐ Monitoring was conducted Per IC Requirements *(provide IC monitoring report to IND sponsor)*

NOTE: *THIS WORKSHEET MUST BE SIGNED BY THE PRINCIPAL INVESTIGATOR.*

ESSENTIAL CLINICAL MONITORING ELEMENTS		
SUBJECT OR FILE IDENTIFICATION No. _____ ***(This form must be completed for each subject file that is selected to be monitored)***		
13 File Management		** Response requires CAPA*
1	Is the most recent protocol version available?	Yes☐ No ☐*
2	If yes, state the protocol version	Version # _____
3	Is a signed FDA Form 1572 and Financial Disclosure documentation available?	Yes☐ No ☐*
4	Is there a *Site Signature and Delegation Log*?	Yes☐ No ☐*
5	Is there a document that assures IRB approval was obtained prior to enrollment of the subjects in the study?	Yes☐ No ☐*
14 Safety		** Response requires CAPA*
6	Were there any occurrences of *AE* or *SAE*'s?	Yes☐ No ☐
	(If "Yes" complete 7-9, if "No" skip 7-9)	
7	Was *AE/SAE* Investigated and documented?	Yes☐ No ☐*
8	Was *AE/SAE* Reported to IRB?	Yes☐ No ☐*
9	Was *AE/SAE* Reported to IND Sponsor?	Yes☐ No ☐*
10	Was there any *AE/SAE* that was missed and not reported?	Yes☐* No ☐
11	Were there any *deviations* to the protocol?	Yes☐ No ☐
12	If "Yes" was deviation reported the IRB and Sponsor?	Yes☐ No ☐*
15 Consent Form		** Response requires CAPA*
13	Was a consent form obtained?	Yes☐ No ☐*
14	If yes, was the most current IRB approved consent form used?	Yes☐ No ☐*
15	If yes, what is the expiration date of the consent form?	Date Consent form filled out_____ Exp. Date of Consent form _____
16	Was the consent form signed and dated by patient or guardian?	Yes☐ No ☐*
17	Was the subject's signature/date on consent form prior to initiation of the study-specific procedure(s)?	Yes☐ No ☐*

18	Was a copy of the signed consent given to subject?	Yes☐ No ☐*
19	If yes, is there documentation in the subject's medical record that the copy was given?	Yes☐ No ☐*
16 Subject Records (Patient Study Binder)		** Response requires CAPA*
20	Are *Source Documents* available and reviewed?	Yes☐ No ☐*
21	If applicable, are the *CRF*s available and verified to ensure accuracy with the source documents?	Yes☐ No ☐* N /A ☐
22	Was the PET Radiopharmaceutical administered per protocol specifications?	Yes☐ No ☐*
23	Is there a document that lists inclusion / exclusion criteria?	Yes☐ No ☐*
24	Did the subject enrolled meet all inclusion / exclusion criteria?	Yes☐ No ☐*
25	Has the subject missed any visits specified in the protocol?	Yes☐ No ☐
26	If yes, were the missed visits and the reason documented?	Yes☐ No ☐*

CAPA (CORRECTIVE AND PREVENTIVE ACTION)

List actions taken to correct deficiencies as a result of this monitoring. This is a tool for quality improvement. Attach additional pages if needed.

INSTITUTE: National Cancer Institute

STUDY NUMBER: 13-C-0193 PRINCIPAL INVESTIGATOR: Electron Kebebew, MD

STUDY TITLE: Evaluation of ^{68}Gallium- DOTATATE PET/CT for Detecting Primary and Metastatic Neuroendocrine Tumors

Continuing Review Approved by the IRB on 12/19/16
Amendment Approved by the IRB on 10/16/17 (J) Date posted to web: 11/10/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

Before a new experimental agent may be made widely available, it must be shown to be safe and effective. A clinical trial is a research study in patients to assess the effectiveness and safety of a new agent. Such trials begin only after extensive testing of the experimental agent in a laboratory.

The purpose of this trial is to determine the accuracy of a new experimental radiolabeled form of the chemotherapeutic drug, ^{68}Gallium-DOTATATE in detecting unknown primary of gastrointestinal and pancreatic neuroendocrine tumors, and whether it can help in performing more complete removal of tumors that require an operation. ^{68}Gallium-DOTATATE will be used for PET/CT imaging. ^{68}Gallium-DOTATATE is not being used as a treatment for your disease. However, images produced by the distribution of this compound in your body will show the tumors that take up ^{68}Gallium -DOTATATE, and also reflects their potential to be treated with Somatostatin based drugs, since both Somatostatin and DOTATATE target the same type of tumor receptors.

Why are you being asked to take part in this study?

This study is open to patients who have or are suspected to have neuroendocrine tumors (functionally active or not) or a family history of neuroendocrine tumors in patients with MEN1 or Von Hippel-Lindau (VHL) or other hormone secreting tumors that are suspected or known to have somatostatin receptors.

How many people will take part in this study?

This study is expected to accrue approximately 390 patients.

Description of Research Study

What will happen if you take part in this research study?

Imaging and Research Samples:

By enrolling is this study, you will be asked to undergo two types of scans. First will be a standard CT scan. The second scan is the investigational scan, a ^{68}Gallium-DOTATATE PET/CT. Prior to your scans you will also have a medical exam and have blood drawn for routine blood tests. Additionally, a blood sample as well as a urine sample will be drawn for research purposes.

The treatment to be received for your disease will not be dictated by this protocol (i.e. you can participate in another therapeutic study, be treated by your local doctor, or receive surgery while participating in this study).

The positron emission tomography/computed tomography (PET/CT) is a type of scan that uses a large donut shaped detection device. The scanner contains crystals that pick up tiny radiation signals given off by radioactive substances (tracers) that have been injected into the vein. The images generated by the scanner show where the radioactive tracer is in the body. The CT portion of the PET/CT is performed with low dose x-rays that go through your body and help us to better localize where the radioactive tracer is concentrating.

On the day of the ^{68}Gallium-DOTATATE PET/CT imaging, you will report to the PET department and one venous line (IV) will be placed in your arm, or other accessible location. In the PET Department you will receive an intravenous injection of ^{68}Gallium-DOTATATE (the study agent) over a few seconds. The entire ^{68}Gallium-DOTATATE PET/CT imaging session is expected to take around one and a half to two hours: from the time of ^{68}Gallium-DOTATATE injection, it takes around 60 minutes for the agent to be distributed in the body until the images can be acquired and approximately 40 minutes are needed to perform the body scan.

We will also collect follow-up information regarding your progress for up to five years after enrollment. We will ask you to return to clinic each year for a medical exam, blood draw for routine blood tests, and a CT scan. Some patients with increasing number of lesions; increase in size of lesions or with small lymph node lesions will be asked to have another ^{68}Gallium-DOTATATE PET/CT scan at the first year of follow-up and then again yearly for up to 5 years from when you started the study. The procedure for this would be exactly the same as described above.

Surgery and Follow Up:

Treatments covered under this study may include surgery to treat your cancer. These treatments will not be experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. You may be asked to sign a separate consent form for any treatment procedures not outlined in this consent.

If you agree to participate in this study, your surgery can be performed at the NIH Clinical Center. Prior to your operation, your surgeon will discuss the specific details of the surgical procedure with you. We will keep some of the tumor tissue that is removed for research studies that help us understand if the imaging agent is useful and to determine if known drug transporters are present within the sample. We will analyze receptor status of tumor samples, the messenger

molecules in the cell and the level of protein. Once all of your questions have been answered, you will be asked to sign a separate consent for the surgery.

If you need an operation, we will use a new technique for detection of tumor tissue using a handheld gamma probe that can detect and measure the amount of activity of ^{68}Gallium-DOTATATE in normal and tumor tissue. This handheld probe is a gamma detection device that will be used to help make sure that tumor is identified during your surgery. This could help the surgeon to better distinguish tumor tissue from scar tissue or normal tissue and to confirm removal of all tumor tissue that is seen on the ^{68}Gallium-DOTATATE whole body scan. This would require an additional injection of ^{68}Gallium-DOTATATE (5 mCi for adults and 3 mCi for children) at 1.5 and 2 hours before the operation.

After your surgery, you may go to the intensive care unit (ICU) for additional monitoring or you may go back to your room on the patient care unit (PCU). You will receive routine care, including pain medications, and you will be given specific information from the doctor and nurses about what to expect after your discharge from the hospital. While you are in the hospital, your doctor will discuss treatment options with you. If additional treatment is necessary, and there is a protocol appropriate for you here, you may choose to be treated at the NIH. If there is not a protocol for you or you prefer to receive treatment elsewhere, we can refer you to another treatment center or to your primary physician.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this imaging agent would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting the study, during study imaging, and for 1 day after you finish study related imaging. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

If you are a woman of childbearing potential:

By signing this consent form, you confirm to the best of your knowledge that you are not pregnant now and you do not intend to become pregnant during this study.

A urine pregnancy test will be done to confirm that you are not pregnant before your participation in this study and also prior to any imaging session.

Risks or Discomforts of Participation

We do not anticipate any adverse events at the dose of drug used in this study, based on the tracer doses of well-known compounds being administered.

The risks to you would be related to the injection of the agent and the small amount of radiation added to the agent. The injection may cause temporary bruising, swelling and/or pain at the needle prick. A small blister of blood called a hematoma may also occur after the needle prick, but is temporary.

The ^{68}Ga-DOTATATE that you receive is investigational and is therefore considered research. This substance is being monitored by the US Food and Drug Administration (FDA), with Peter Herscovitch, M.D. as the Sponsor. Both the Sponsor and the FDA have access to the medical records of research subjects.

This research study involves exposure to radiation from up to six over a five year period, if indicated by your doctor ^{68}Ga-DOTATATE PET/CT scans.

This radiation exposure is not required for your medical care and is for research purposes only. For an adult the amount of radiation you will receive in this study is 1.6 rem per year, (if receiving two ^{68}Ga-DOTATATE injections in case of surgery, otherwise 1.1 rem per year with one ^{68}Ga-DOTATATE PET/CT scan). For a child between the ages of 15 and 18 the amount of radiation in this study is 0.40 rem per year (if receiving two ^{68}Ga-DOTATATE injections in case of surgery, otherwise 0.30 rem per year with one ^{68}Ga-DOTATATE PET/CT scan). For a child between the ages of 10 and 14 the amount of radiation in this study is 0.45 rem (if receiving two ^{68}Ga-DOTATATE injections in case of surgery, otherwise 0.35 rem per year with one ^{68}Ga-DOTATATE PET/CT scan). This is below the guideline of 5 rem per year for adults and 0.5 rem for children allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

As mentioned earlier, you will need to keep very still under the nuclear medicine camera for a period of about 70 minutes for the longest scan, which you may find slightly uncomfortable. You may need to keep your arms over your head for some of the imaging procedures, which may make your shoulders sore.

There is also the possibility that there may be unforeseen risks associated with this agent, about which nothing is yet known. Any new findings that may affect your decision to remain in the study will be provided to you and your doctor.

What side effects or risks can I expect from being in this study?

Based on known toxicity and low administered dose, no adverse reactions are expected. However, if infusion related allergic reaction is encountered, supportive care will be provided immediately.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental agent is better at detecting tumors in your body. If you undergo surgery, we hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. Because there is not much information about the agent's effect, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have similar tumors.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

You are not obligated to participate in this study. If you decide not to participate, it will not alter your planned treatment in a different protocol or with your local doctor.

Please talk to your doctor about this and other options.

Research Subject's Rights

Participation in this research study is voluntary and you can withdraw at any time. We encourage you to ask questions so you can make the most informed decisions during your participation in this study. Refusal to participate will not result in penalty or less benefits to which you are otherwise entitled.

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.

- Medicines that are not part of the study will not be provided for by the Clinical Center, NIH.

- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- The study Sponsor, Dr. Peter Herscovitch or his agent(s)

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Stopping Study Participation

Your doctor may decide to stop your participation in the study for the following reasons:

- if he/she believes that it is in your best interest
- if the Sponsor can no longer make the study agent
- if you have side effects that your doctor thinks are too severe

In this case, you will be informed of the reason the imaging is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to collaborators or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Electron Kebebew, M.D., Building 10, Room 4-5952, Telephone: 240-760-6153. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative — Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian — Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian — Date — Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM DECEMBER 19, 2016 THROUGH DECEMBER 18, 2017.

Signature of Investigator — Date

Print Name

Signature of Witness — Date

Print Name