

**Comparator Study of <sup>68</sup>Ga-DOTATOC PET/CT with Octreoscan + high-resolution, contrast-enhanced CT for diagnosis and staging in neuroendocrine tumors and other somatostatin receptor positive tumors**

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**Appendices: CRFs attached as separate file in HawkIRB**

- I. Sample Case Report Forms
- II. Data Safety Monitoring Plan

**Summary of Changes to version 9 dated 3/26/14**

Title page	Updated version and date
Table of Content	Updated page numbers
Safety section protocol and DSMP	Updated to current HCCC DSMC risk level 2 language

## Project Goal

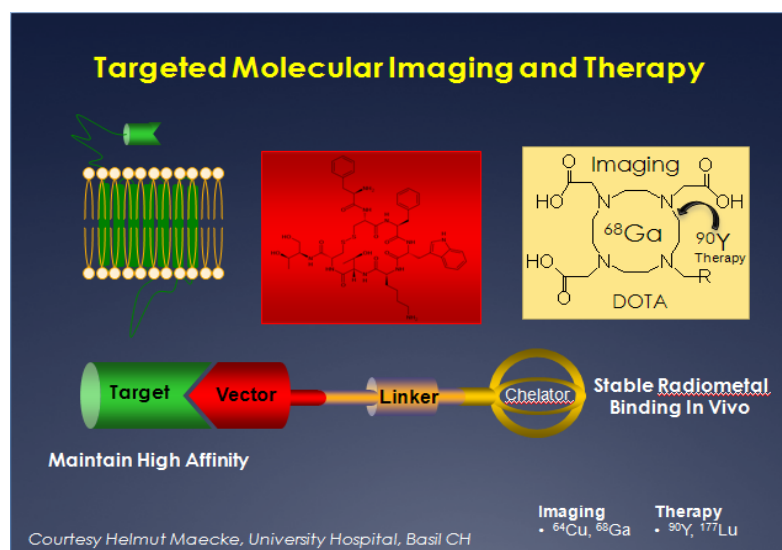
**Compare Sensitivity and specificity of <sup>68</sup>Ga-DOTATOC PET/CT with Octreoscan + high-resolution, contrast-enhanced CT for diagnosis and staging in neuroendocrine tumors and other somatostatin receptor positive tumors**

### 1. Introduction:

#### Somatostatin Receptor Positive Tumors

Neuroendocrine tumors are solid malignant tumors that arise from dispersed neuroendocrine cells found throughout the body. Gastroenteropancreatic neuroendocrine tumors (NETs) can be divided into two groups: Carcinoid tumors that may arise from the lungs, stomach, small bowel or colon and pancreatic neuroendocrine tumors (also known as pancreatic islet cell tumors). The clinical behavior of NETs is extremely variable; some may cause hormone hypersecretion and others may not, the majority of them are slow-growing tumors (well-differentiated NETs), whereas some NETs are highly aggressive (poorly differentiated NETs). The incidence of NETs is increasing, from 1.1/100,000 per year in 1973 to 5.3/100,000 per year in 2004<sup>1</sup>. Among NETs, 25% have distant metastases and 25% have regional involvement at the time of initial diagnosis<sup>1</sup>. Other tumors that express high levels of somatostatin receptors include neuroblastoma, medulloblastoma, and Ewing's sarcoma<sup>2-4</sup>.

The radiological detection and staging of these tumors is challenging and requires a multimodality approach. Somatostatin receptor imaging with In-111 Pentetreotide (OctreoScan) and multiphase CT are the most commonly used modalities although the use of endoscopic ultrasound and MRI is also increasing. Surgery is the only curative option for NETs. However, curative surgery in malignant NET is possible in less than 30% of patients with recurrence identified in the majority of patients as late as 15 years after initial surgery. Treatment with somatostatin analogs, which include the short acting subcutaneous and long acting release (LAR) octreotide, are effective in stabilizing NETs and have been recently demonstrated to prolong the time to progression of disease<sup>5</sup>. Chemotherapy is generally not effective in low grade NETs, but it may be helpful in high grade and pancreatic NETs. On the other hand, neuroblastoma, medulloblastoma, and Ewing's sarcoma are initially responsive to chemotherapy, but relapses are common and salvage therapies are not very effective, resulting in <30% overall survival at 5 years<sup>6-8</sup>.

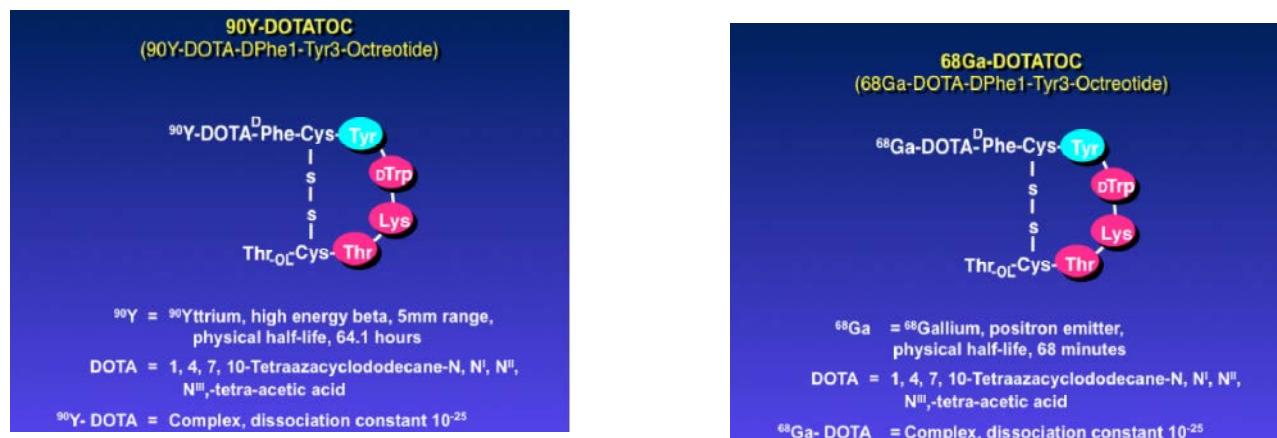


**Figure 1:** Conceptual representation of targeted molecular imaging and therapy of cancerous tumors. A cell surface receptor is identified that is upregulated in cancerous tumor cell relative to normal surrounding tissue and organs. A peptide vector is developed that binds with high affinity and specificity to the molecular target. A chelator is added to the targeting vector via a molecular linker. The chelator can be used to couple a positron emitter as the reporter signal for PET, or with a beta emitting radionuclide (e.g., <sup>90</sup>Y) for molecular therapy. To be effective, the high binding affinity of the vector for the target antigen and the stable (high specific activity) radiometallation must be maintained after placement of the chemical linker.

### Somatostatin Receptor Targeted Imaging and Therapy

Tumors that express somatostatin receptors can be targeted with radiolabeled somatostatin analogues for imaging and treatment (Figure 1). Somatostatin receptor gamma camera imaging with In-111 DTPA-octreotide (OctreoScan) targeting somatostatin receptor 2 (sstr2), is used routinely for imaging of neuroendocrine tumors with a detection rate >90% for well-differentiated carcinoid tumors and majority of pancreatic NETs, but only a 50% detection rate for insulinomas, which may show a weaker expression of sstr2<sup>9</sup>.

Given the clinical efficacy of this radiolabeled peptide as a diagnostic agent, studies to test if therapeutic radiation could be targeted to tumors in a similar manner was a logical next step. Attempts to utilize In-111 DTPA Octreotide as a therapeutic agent have been minimally effective due to short range of auger electrons utilized in this therapy. The efficacy of this treatment was improved with the development of somatostatin analogues labeled with beta emitting radioisotopes. Further studies have identified DOTA as a superior chelator compared to DTPA, increasing the stability and receptor targeting of somatostatin analogues<sup>10</sup>. There is now a large clinical experience with Yttrium-90 DOTA-tyr3-Octreotide peptide radioreceptor therapy (PRRT) in Europe, primarily in adults with neuroendocrine tumors<sup>11</sup>. An international Phase II clinical trial then followed and included several trial sites in the United States, notably the University of Iowa, where we entered 40 subjects<sup>12</sup>. With its low toxicity profile, the significant improvement in symptoms and quality of life and the lack of effective alternative therapies, PRRT has been suggested as possible first-line therapy in adult patients with gastroenteropancreatic neuroendocrine tumor. Recent data have also demonstrated a significant survival benefit with PRRT compared to historical controls in this population. We have also now conducted a Phase I trial of <sup>90</sup>Y-DOTA-tyr3-Octreotide in children and young adults at the University of Iowa, which also shows promise of efficacy of this treatment in pediatric patient population<sup>13</sup>. We now propose a new imaging agent for use in diagnosis and therapy of Somatostatin receptor positive tumors as shown in Figure 2.



**Figure 2** Chemical identity of [<sup>68</sup>Ga]DOTATOC IND # 114,398 with current IND #61,907 compound [<sup>90</sup>Y]DOTATOC

### Somatostatin Receptor PET Imaging with Ga-68 DOTA<sup>0</sup>-Tyr<sup>3</sup>-octreotide

More recently, positron emission tomography (PET) radiopharmaceuticals have been developed that can be labeled with Gallium-68 (Ga-68). Gallium-68 is a generator product with a half-life of 68 min (compared to 67 hours for In-111 in OctreoScan). The parent nuclide of Ga-68 is Germanium-68, which has a half-life of 270.8 days. Ga-68 decays by 89% through positron emission and 11% by electron capture. Its parent, A number of <sup>68</sup>Ga-DOTA-conjugated peptides have been introduced, including <sup>68</sup>Ga-DOTA<sup>0</sup>-Tyr<sup>3</sup>]octreotide (**<sup>68</sup>Ga-DOTATOC**), Ga-68 DOTA<sup>0</sup>-1Na<sup>3</sup>-octreotide (<sup>68</sup>Ga-DOTANOC) and <sup>68</sup>Ga-DOTA<sup>0</sup>-Tyr<sup>3</sup>]octreotate (<sup>68</sup>Ga-DOTATATE). All of these radiolabeled peptides bind to sstr2, although DOTANOC also binds to sstr 3 and sstr 5, and DOTATOC to sstr5<sup>14</sup>. The primary advantage of Ga-68 based somatostatin receptor PET imaging over OctreoScan SPECT is the higher imaging resolution and accurate quantification of uptake due to robust attenuation correction. The improved resolution and quantitation of uptake obtained with <sup>68</sup>Ga-DOTATOC PET/CT should provide a more accurate

assessment of somatostatin receptor density, which will lead to a more accurate prediction of treatment response to somatostatin analogues. A recent study from Europe comparing <sup>68</sup>Ga-DOTATOC PET/CT with Octreoscan found <sup>68</sup>Ga-DOTATOC PET/CT to be superior in detection of skeletal and pulmonary involvement of neuroendocrine tumors<sup>15</sup>. We have recently published an analysis of the reproducibility of sequential <sup>68</sup>Ga-DOTATOC PET/CT imaging in patients with known neuroendocrine tumors<sup>16</sup>

## **2. Rationale and overall study design**

### Rationale:

The purpose of this clinical trial is to compare the efficacy of <sup>68</sup>Ga-DOTATOC PET/CT in diagnosis and staging of somatostatin receptor positive tumors, including, but not limited to neuroendocrine tumors, neuroblastoma, and medulloblastoma, with the current standard of care in the United States, namely, an Octreoscan + a high-resolution, contrast-enhanced CT.

If efficacy of <sup>68</sup>Ga-DOTATOC PET imaging is equivalent or superior, it would replace single photon emission tomography (SPECT) imaging with Octreoscan over which it has known advantages. Whereas, Octreoscan™ uses a 222 MBq imaging dose of Indium (2.8 day half life) resulting in an effective dose equivalent (HE) equal to 2.61 rads, <sup>68</sup>Ga-DOTATOC (68 min half life) uses 185 MBq with an effective dose equivalent of 0.46 rads. In addition, <sup>68</sup>Ga-DOTATOC PET/CT can be completed within 2 hours compared to an Octreoscan™ which requires 3 visits over 24 hours, making <sup>68</sup>Ga-DOTATOC a much more convenient imaging choice for patients. The data obtained in this <sup>68</sup>Ga-DOTATOC PET study will be used to support the use of <sup>68</sup>Ga-DOTATOC PET for diagnosis and staging in patients with suspected or proven somatostatin receptor positive tumors.

## **Overall Study Goal and Study Design**

### Project Goal

This study is planned to compare efficacy of [<sup>68</sup>Ga]-DOTA-tyr3-Octreotide (<sup>68</sup>Ga-DOTATOC) PET/CT with Octreoscan + high-resolution, contrast-enhanced CT for diagnosis and staging in patients with somatostatin receptor expressing tumors.

### Project Design

This is a prospective, single center, open-label study in subjects with known neuroendocrine tumors and other Somatostatin receptor positive tumors to evaluate the accuracy of <sup>68</sup>Ga-DOTATOC PET-CT. Eligible participants will have an Octreoscan and a high-resolution contrast-enhanced CT within 120 days (+/- 12 days to allow for scheduling conflicts and travel) of the <sup>68</sup>Ga-DOTATOC PET-CT. All subjects will undergo baseline assessments at enrollment. Study participants will receive <sup>68</sup>Ga-DOTATOC and undergo a PET/CT imaging study. A second <sup>68</sup>Ga-DOTATOC PET-CT will be obtained in patients if the lesions of the first scan cannot be confirmed with histology and/or other imaging modalities.

## **Participant Enrollment**

Participants will be recruited from the University of Iowa Comprehensive Cancer Center Clinics and the University of Iowa Children's Hospital. Participants who will be approached regarding the study are those individuals who are being seen for known or suspected malignancies. The study will be posted on clinicaltrials.gov as another recruitment option.

## **Schema**

### Informed Consent

Review pathology report, Octreoscan, CT, and laboratory tests  
Physical exam with vital signs  
Blood tests (CBC, differential, AST, ALT, bilirubin, BUN, creatinine)

Pregnancy test if indicated  
Injection of <sup>68</sup>Ga-DOTATOC  
PET/CT scan  
vital signs

Phone call follow-up 18-36 hrs after PET/CT

Repeat blood tests (AST, ALT, bilirubin, BUN, creatinine) within 7 days after PET/CT scan

Patients may undergo second scan 3-6 months (+/- 18 days to allow for scheduling conflicts and travel) after first <sup>68</sup>Ga-DOTATOC PET/CT scan using above schedule.

## 2. Clinical Protocol

### Inclusion Criteria:

- Signed informed consent.
- Age ≥ 2 years.
- Biopsy proven neuroendocrine tumor, neuroblastoma, medulloblastoma, or other somatostatin receptor positive tumor.
- Off Sandostatin-LAR >4 weeks and off immediate release (subcutaneous) for 12 hrs prior to <sup>68</sup>Ga-DOTATOC PET-CT.
- Karnofsky performance status or Lansky Play Scale status of ≥ 50 (or ECOG/WHO equivalent).
- Subject is male; or is a female who is either pre-menarchal, surgically sterile (has had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (> 1 years without menses), non-lactating, or of childbearing potential for whom a serum pregnancy test (with the results known prior to investigational product administration) is negative. A negative serum pregnancy test will be required for all female subjects with child bearing potential. If a false pregnancy test is suspected, e.g., perimenopausal condition, an obstetrician will be consulted to determine if she is/is capable of becoming pregnant.
- No therapy other than Sandostatin since last Octreoscan + diagnostic CT;
- Fresh frozen (recommended) or paraffin fixed (required) specimen of primary or metastases available for RNA and IHC;

### Exclusion Criteria:

- Pregnancy or breast feeding
- Surgical resection, chemotherapy, radiation therapy, or biologic therapy since last Octreoscan + CT. Continuation of the same dose of Sandostatin-LAR or subcutaneous Sandostatin is allowed.
- Medical condition uncontrolled by treatment making completion of study unlikely.
- Weight more than 400 pounds (Subjects who weigh more than 400 pounds will not be able to fit inside the imaging machines).
- Inability to lie still for the entire imaging time (e.g. cough, severe arthritis, etc.)
- Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc.)
- Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance

## Procedures

### Informed Consent

Subjects meeting eligibility criteria will be consented. After consent, subjects are considered actively enrolled in the study and a study log will be maintained. Record of consent will be scanned into the patient's electronic chart.

<b>Table 1. Schedule of Study Events</b>					
	<b>Visit 1<sup>a</sup> (-30 to -1 day)</b>	<b>Scan 1<sup>b</sup></b>	<b>1-7 days</b>	<b>Scan 2</b>	<b>1-7 days</b>
Informed consent	X				
Medical history	X			X	
Physical examination	X <sup>c</sup>	X		X	
Concomitant meds	X	X		X	
Blood pressure, temp, respiratory rate, heart rate, weight	X	X		X	
CBC, differential		X		X	
, AST, ALT, bilirubin, BUN, creatinine		X	X	X	X
Pregnancy test <sup>d</sup>	X	X		X	
<sup>68</sup> Ga-DOTATOC PET/CT		X		X	
Adverse events	X	X	X	X	X
Octreoscan and contrast CT (or MRI) within 120 days of Ga-68 DOTATOC PET/CT					
<u>a</u> Screening visit occurs within 30 days of Ga-68 DOTATOC PET/CT					
<u>b</u> Baseline procedures must be performed no more than 7 days prior to study drug.					
<u>c</u> Visit 1 physical exam to include height and performance status.					
<u>d</u> A urine pregnancy test may be done in PET if Visit 1 and Scan 1 are on separate days.					
Screening results must be available and baseline procedures performed before the first dose of study drug is administered. To avoid repeat tests, some screening values may be counted as baseline values if obtained within specified time window.					

**Physical Examination and Medical History**

Physical examination will be performed to ensure suitability according to the inclusion and exclusion criteria at screening and baseline and to document the health status and toxicity at the time points specified in the Schedule of Events (**Table 1**).

The physical examination comprises measurement of height and body weight, vital signs of temperature, pulse, respiratory rate, and blood pressure. A medical history will be recorded at screening and prior to second scan. The medical history will elicit information concerning existing medical conditions, major illnesses, and related surgical procedures. Any prescribed or over-the counter medications that the subject received within the past 30 days should be recorded on the case report form (Appendix IV).

**Pregnancy Test**

Female subjects of childbearing potential will have a pregnancy test (serum) before exposure to research-related radiation. A woman who is pregnant may not participate in this study and must tell us if she may have become pregnant during the previous 14 days because the pregnancy test is unreliable during this time. If a false pregnancy test is suspected, e.g., perimenopausal condition, an obstetrician will be consulted to determine if she is/is capable of becoming pregnant.

### **68Ga-DOTATOC PET/CT Scan**

Study participants will undergo the <sup>68</sup>Ga-DOTATOC PET/CT after all screening and baseline assessments have been completed. The dose will be injected via IV access lines. All investigational scans will be read by at least two experienced board-certified nuclear medicine physicians with established expertise in PET/CT. Readings will be performed independently and blinded to the other physician's interpretation. A data form will be completed prospectively of the site(s) of the primary tumor (if visible/present) and metastases.

Interpretation discrepancies will be resolved by consensus of the two interpreting physicians or, in event of failure to reconcile, by a third nuclear medicine physician. The final report will then be provided for clinical management. Any controversies will be clearly communicated to the clinical care givers and for data analysis. CT scans of PET-CT will be done for anatomic localization and attenuation correction using a low tube current.

### **Investigational Radiopharmaceutical Administration**

<sup>68</sup>Ga-DOTATOC will be administered intravenously in conjunction with the PET/CT scan. The one-time nominal injected dose will be 3-5 mCi containing <50 µg <sup>68</sup>Ga-DOTATOC (estimated, allowing for adherence of peptide to glassware or syringes, a portion of the 50 µg original quantity used for QC, etc). The normal adult dose will be 4 mCi with adjustments made for smaller body size such that the dose will be 0.043 mCi/kg with a minimum dose of 0.3 mCi and a maximum dose of 3 mCi in children <18 years old.

<sup>68</sup>Ga-DOTATOC is produced by research chemists who are experienced in clinical and investigational radiopharmacy in the University of Iowa PET Center. The University of Iowa PET Center staff will conduct the quality control and will approve the final preparation following USP <823> standards. Before final release of the agent for administration, release criteria set forth by the European pharmacopeia monograph for Gallium (<sup>68</sup>Ga) Edotreotide <sup>68</sup>Ga-DOTATOC injection will be verified. Bacterial endotoxin testing as well as radiochemical and radionuclidic purity testing will also be performed prior to release. In addition to careful observation and monitoring of the patient within the PET/CT area for one hour after injection until scan completion (an additional approximately 40 – 45 minutes), the patient will be closely monitored in the PET/CT area or recovery room for a total of 2 hours after injection of the radiopharmaceutical. The subject or his/her guardian will be verbally asked to identify any symptoms or other change in status that might indicate an adverse reaction to the investigational radiopharmaceutical, and will be released only if no adverse events are observed (objectively or subjectively). The following day, all subjects will be contacted by phone and again asked if untoward/adverse events occurred after release. Subjects will be required to have repeat blood tests within 1 week of the PET/CT. This can be done at University of Iowa Hospitals or at a local physician's office. Information from a local visit would need to be faxed to the University of Iowa. Any observed adverse events will, of course, be treated immediately and appropriately, and reported to the University of Iowa IRB and the FDA in accordance with established guidelines.

### **Scan Interpretation:**

Readers of the investigational <sup>68</sup>Ga-DOTATOC PET/CT will be blinded to the patient's identity and to any other clinical information prior to initial interpretation. A board certified nuclear medicine physician, experienced and credentialed in interpretation of clinical PET/CT scan, will independently report all locations of suspected tumor deposits without discussion with other healthcare providers or correlation with other imaging. In addition to localizing all areas of tumor, quantification of size and uptake of up to 5 "target" lesions will be performed (no more than two in a given organ), with SUV and cross sectional measurements in long axis and short axis, in mm, recorded for each lesion visible on CT. All of these interpretations will be retained for statistical analysis. Readers will then be asked to review all other available imaging (see next paragraph) to see if there are sites of tumor seen on conventional imaging not seen with <sup>68</sup>Ga-DOTATOC on the initial interpretation, and, if so, to determine if this impacted



treatment decisions. These results will be recorded for statistical analysis. After the investigational <sup>68</sup>Ga-DOTATOC PET/CT has been independently interpreted, comparison will be made with other, conventional imaging (CI), as available. CI used for comparison will include CT scans, MRI scans, Octreoscans, ultrasounds and x-ray plain films. Part of data analysis specific to imaging will include:  Whether there were sites of tumor seen with <sup>68</sup>Ga-DOTATOC PET/CT not seen with CI, and, if so, these data will be recorded for statistical analysis  Whether or not the <sup>68</sup>Ga-DOTATOC PET/CT resulted in a change in stage relative to CI, and, if so, whether it would be up- vs. down- staging  Whether or not the <sup>68</sup>Ga-DOTATOC PET/CT scan result caused the clinical care givers to change treatment, e.g. change within modality (e.g. change Sandostatin dose, request surgery consult) or across modalities (e.g. add chemotherapy or radiation therapy to surgery, etc.).

### Data Analysis:

<sup>68</sup>Ga-DOTATOC PET scans will be compared to a composite gold -standard that includes conventional imaging modalities and clinical follow-up to determine the sensitivity and specificity of <sup>68</sup>Ga-DOTATOC PET:

A lesion visualized on <sup>68</sup>Ga-DOTATOC PET/CT will be considered as true positive if

- 1) proven by biopsy OR
- 2) visualized on baseline Octreoscan AND diagnostic CT scan OR
- 3) visualized on Octreoscan  OR diagnostic CT AND concordant NET biomarkers are positive OR
- 4) <sup>68</sup>Ga-DOTATOC PET positive bone lesion not visualized on Octreoscan OR diagnostic CT is clearly visible on bone scan or MRI OR
- 5) <sup>68</sup>Ga-DOTATOC PET positive lesion not proven with 1 to 4 above shows increase in <sup>68</sup>Ga-DOTATOC PET/CT on a 3-6-month follow-up scan (+/- 18 days to allow for scheduling conflicts and travel) with concordant NET biomarkers. If a <sup>68</sup>Ga-DOTATOC positive lesion cannot be confirmed with any of these five parameters, it will be considered false-positive.

A negative <sup>68</sup>Ga-DOTATOC PET/CT will be considered true negative if no lesions are found on Octreoscan AND diagnostic CT and NET tumor biomarkers are negative. A negative <sup>68</sup>Ga-DOTATOC PET/CT will be considered false negative if :

- 1) a concordant lesion is found on Octreoscan and diagnostic CT at baseline OR
- 2) a NET lesion is confirmed by pathology OR
- 3) a lesion is identified on diagnostic CT with concordant biomarkers or shows interval growth on followup CT OR
- 4) osseous metastases are identified on MRI or bone scan.

### Receptor analysis

Tissues obtained for the patients will be analyzed for the presence of somatostatin receptor 2 by immunohistochemistry and/or RT-PCR. Positivity and grade will be determined by a board-certified pathologist. These results will be correlated with the signal intensity for the <sup>68</sup>Ga-DOTATOC PET/CT.

### Statistical Considerations

The distribution of patients will be an important element of statistical consideration. Several types of patients will be studied, including patients with:

- Primary pancreatic, small bowel, or lung neuroendocrine tumor
- Metastatic pancreatic, small bowel or lung neuroendocrine tumor
- Primary or metastatic neuroblastoma
- Primary or metastatic medulloblastoma
- Primary or metastatic pheochromocytoma

Given the distribution of patients seen at the University of Iowa Hospitals, an excellent distribution of patients will be enrolled. We predict that with a total of 112 subjects, each of the above types of

diagnoses will be captured and accuracy of the <sup>68</sup>Ga-DOTATOC PET/CT can be adequately studied. We will observe for adverse events related to the use of the <sup>68</sup>Ga-DOTATOC radiopharmaceutical in accordance with NCI toxicity guidelines (described below) in order to provide the FDA and ourselves with important, traceable toxicity/safety data regarding the use of this investigational radiopharmaceutical. In those patients with available conventional imaging (Octreoscan, high-resolution, contrast CT or MRI), we will determine if the <sup>68</sup>Ga-DOTATOC PET/CT scan alters care of patients and whether or not conventional imaging demonstrated negative or equivocal evidence of tumor size and location in the same patients. Many of our patients will be referred from outside centers with conventional imaging (CT, MRI and <sup>111</sup>In-Octreotide scans) already accomplished. We will assess for an impact on treatment by determining if a given patient's care is altered after the results of the <sup>68</sup>Ga-DOTATOC PET/CT scan are available.

For those patients who have available CT, MRI or Octreoscan, we will determine equivalence of conventional imaging and <sup>68</sup>Ga-DOTATOC PET using percentage of concordance in tumor detection. We hypothesize that less than 80% agreement on their assessment would be inconclusive while more than 90% agreement on their assessment would favor equivalence. We define an indicator variable for <sup>68</sup>Ga-DOTATOC PET/CT findings (+/-) and another indicator variable for Octreoscan findings (+/-). Positive findings are labeled (+) while negative findings are (-); with concordance <sup>68</sup>Ga-DOTATOC PET/CT vs. Octreoscan occurring at the combinations (++) and (--), and discordance occurring at (+/-) or (-/+).

Since the same patient is measured under both tumor detection methods (conventional imaging and <sup>68</sup>Ga-DOTATOC PET/CT), we base our sample size and power justification on the proportion of concordance and on the proportion of discordance. This outcome is of direct benefit to patient population. This analysis requires 112 patients to decide whether the proportion of agreement between the two assessment methods is less than or equal to 80% or greater than or equal to 90%. If 97 or more subjects result in the same decision on both <sup>68</sup>Ga-DOTATOC PET/CT and conventional imaging, the null hypothesis that  $P \leq 80\%$  would be rejected in favor of the alternative. The expected error rate is  $\alpha = 0.05$  and the actual error rate of 0.047. If this number of subjects with concordant decision is 96 or less, the hypothesis that  $P \geq 90\%$  is rejected with a target error rate of 10% and an actual error rate of 0.092. The power of the test is 90%.

In case the null of  $P \leq 80\%$  is accepted, we have at least 20% chance of assessing discordance. This percentage (~22 subjects) is then used to search for false positives and false negatives. Pilot data suggests more subjects may fall within the category +/- (i.e. positive <sup>68</sup>Ga-DOTATOC PET/CT, negative Octreoscan).

**Note:** There is a source of bias in this design. Subjects receive treatment based on positive findings from Octreoscan + diagnostic CT, the composite gold standard, regardless of their discordance with [<sup>68</sup>Ga]DOTATOC PET/CT. Bias came about because the cohort -/+ (i.e. <sup>68</sup>Ga-DOTATOC PET/CT (-) and composite gold standard (+)) would receive treatment regardless of <sup>68</sup>Ga-DOTATOC PET/CT finding. This bias should not create a commotion because the scenario -/+ would be rare based on pilot finding. The discordance +/- (i.e. <sup>68</sup>Ga-DOTATOC PET/CT (+) and composite gold standard (-)) is more important at showing the advantage of <sup>68</sup>Ga-DOTATOC PET/CT. This discordance would yield a population greater than 22 if concordance is less than 80% and a population <22 otherwise.

Binomial exact tests would be used on this discordant population after biopsy and after 6-month follow up to detect whether the proportion discovered after biopsy (or follow up) is significantly smaller or comparable to the population claimed by <sup>68</sup>Ga-DOTATOC PET/CT findings. This will also serve as false positive rate assessment if not confirmed at follow up. On a more general note for discordance/concordance study design, a sample of size 112 (or a set of 112 pairs of assessment) will achieve 99% power to detect an odds ratio of 12.33 using a two-sided McNemar test with a significance level 0.05. The odds ratio is equivalent to a difference between 2 paired proportions of 17% which occurs when the proportion of -/+ is 1.5% (i.e. <sup>68</sup>Ga-DOTATOC PET/CT negative; composite gold standard positive) and the proportion in +/- is 18.5% (i.e. <sup>68</sup>Ga-DOTATOC PET/CT positive; composite gold standard negative), and the total discordance is 20%.

**Power Table**

Sample Size	Power	Odds Ratio	-/+ Rate	+/-Rate	Alpha
112	99%	12.33	1.5%	18.5%	0.05
112	96%	7.00	2.5%	17.5%	0.05
112	86%	4.71	3.5%	16.5%	0.05
112	79%	4.00	4.0%	16.0%	0.05

**Risks**

**Risks of Study Drug**

**Research radiation dose estimate:** The effective whole-body dose of the <sup>68</sup>Ga-DOTATOC PET/CT is approximately 1.6 rem<sup>17</sup>, less than the radiation dose from a conventional <sup>18</sup>F-FDG PET/CT scan of about 2.4 rem, assuming the standard use of a “low-dose” CT for anatomic localization and attenuation correction, as described in our proposed imaging protocol. The U.S. national annual background dose for humans is approximately 0.36 rem. The maximum annual permissible whole body radiation dose to a career radiation worker (e.g., a radiologist, nuclear medicine technologist, etc.) is 5.0 rem. Thus, the one-time dose to the patient for the investigational PET/CT will be approximately one-third of the annual permissible dose to a career radiation worker and about 5 years’ worth of background radiation in the US. Given the average age of the patients in this proposed investigation (about 60 years of age), the increased risk to the patient, who will have a known, current life-threatening malignancy, for a second, radiation-induced malignancy from this investigational radiation exposure is extremely low (estimated < 1%). Given the risk of death from either delay in diagnosis or under-treatment of these known malignancies, we feel the added radiation burden to the patient is well within the patient’s best interest if <sup>68</sup>Ga-DOTATOC PET/CT imaging adds value.

**Risks of Study Procedures**

Risks of Investigational PET/CT: An adverse reaction to the investigational radiopharmaceutical is possible though not reported. Additional risks include radiation exposure from the investigational PET/CT scan (discussed above), dosage infiltration, risks from IV access, blood tests, and the inconvenience of the investigational PET/CT scan.

Children may require sedation or anesthesia to remain still during the PET scanning procedure. The risks of sedation include a reaction to the medication used for sedation or anesthesia. If anesthesia is required, there is a risk of injury to the throat or airways from insertion of the breathing tube.

**Reporting Adverse Events or Unanticipated Problems involving Risk to Subjects or Others**

**Adverse Event Terminology**

**1. Adverse Event**

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

- Subject deterioration due to the primary illness at the onset of the trial
- Intercurrent illnesses
- Drug interactions
- Events related or possibly related to concomitant medications
- Abnormal laboratory values or changes of vital signs, as well as significant shifts from baseline within the range of normal, considered to be clinically significant by the Investigator.

**2. Adverse Drug Reaction**

In the pre-approval clinical experience with a new medicinal product or its new usage, particularly as the therapeutic dose(s) may not be established, an adverse drug reaction is defined as:

*All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADR).*

### **3. Unexpected Adverse Drug Reaction**

An unexpected ADR is: *An adverse drug reaction, the nature or severity of which is not consistent with the applicable product information, also known as reference safety information.*

### **4. Serious Adverse Event/Serious Adverse Drug Experience**

During clinical investigations, serious AEs may occur. If the event is suspected to be drug-related, the event may be significant enough to lead to important changes in the way the medicinal product is developed (e.g. change in dose, population, needed monitoring, consent forms). This is particularly true for reactions, which, in their most severe forms, threaten life or function. A serious AE (SAE) or serious adverse drug experience (SADE) is any untoward medical occurrence that:

- Results in death.
- Is life-threatening. 'Life-threatening' refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICHE6).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/ incapacity (as per reporter's opinion).
- Is a congenital anomaly/birth defect.
- Is another medically important condition. Important medical conditions that may not result in death, be life-threatening or require hospitalization may be considered as SAEs or SADEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse
- [Code of Federal Regulations Title 21, Volume 5, 21CFR312.32, revised April 1, 2006].
- Please note: Serious is not synonymous with severe. An event may be severe (e.g., severe headache) but still be of minor medical significance. Serious refers to an event that poses a threat to the subject's life or functioning.

### **5. Assigning Severity to an Adverse Event**

Severity of adverse events will be graded according to NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) which is available at <http://ctep.cancer.gov/reporting/ctc.html>.

### **6. Assigning Relationship of Adverse Event to Study Drug (Causality)**

The Investigator will determine the relationship of each 'probably related'. Descriptions of the three classification categories are as follows:

#### **Not Related**

Exposure to study drug has not occurred; administration of study drug and the adverse event are not reasonably related in time; or the AE is considered by the Investigator to be due to a pre-existing condition, a known manifestation of the target disease, a recurrent condition, or is likely explained by environmental or diagnostic therapeutic factors or was preexisting and did not deteriorate.

#### **Possibly Related**

The AE occurred during or within a reasonable period of time after administration of the study drug, or a pre-existing event worsened within an appropriate period of time after administration of study drug, but the AE could be explained equally well by factors or causes other than exposure to the study drug. This

category will also be used if there is a lack of information, or insufficient or conflicting evidence exists for classifying the causality of the AE.

### **Probably Related**

The AE occurred during or within a reasonable period of time after administration of the study drug or a pre-existing event worsened within an appropriate period of time after administration of study drug, and at least one of the following criteria is applicable:

- the event could not be explained by the clinical condition or history of the subject, environmental or toxic factors, or other diagnostic or therapeutic measures;
- the event was an expected ADR associated with study treatment or a class-labeled drug effect;
- the AE subsided or disappeared after withdrawal or dose reduction of study treatment; or
- the AE recurred after re-exposure to study treatment.

### **Adverse Event Recording and Reporting**

#### **Adverse Event Recording**

At baseline, all SAEs and study-related AEs since signing of the Informed Consent Form will be recorded. After initial study drug administration, all AEs will be recorded. Each AE occurring to a subject, either spontaneously revealed by the subject or observed by the Investigator, whether believed by the Investigator to be related or unrelated to the study drug, must be recorded on the AE Case Report Form and on the subject's file. Type and severity of AEs will be reported by the subjects without being given a list of fixed symptoms beforehand. The Investigator will also determine the relationship of any AE to study drug (causality) and record it on the appropriate section of the AE CRF as well as their severity, time of onset, duration, and the precautions carried out, and whether or not the event meets one or more of the definitions of an SAE. Laboratory results will be recorded on the case report form and the investigator will indicate whether abnormal results (high or low) are clinical or not clinically significant. Clinically significant laboratory abnormalities will be entered on the 'Adverse Event Form' of the CRF. Clinically significant changes in vital signs (e.g., tachycardia) or other clinically significant changes observed by the physician will be entered in the appropriate CRF. These AEs will also be noted on the 'Adverse Event Form' of the CRF as well as in the subject file.

#### **Serious Adverse Event Reporting**

All SAEs must be reported promptly to the PI and will follow IRB and IND regulatory reporting requirements. SAEs should be followed to resolution, even if this is after the study reporting period.

#### **Data and Safety Monitoring**

The Data Safety Monitoring Plan for this study (see Appendix II) is written to ensure the safety of subjects and to verify the validity and integrity of the data.

#### **Assessing Toxicity:**

Toxicity will be graded according to NCI's Common Toxicity Criteria (CTCAE v4). The principal investigator will be responsible for determining the attribution of toxicity as it is related to the investigational drug. All grades of toxicity will be noted and reported appropriately.

#### **Adverse Event Reporting:**

An adverse event (AE) is defined in the *CTEP, NCI Guidelines* [2005] as "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure (attribution of unrelated, unlikely, possible, probably or definite)."

All adverse events associated with the experimental procedures will be reported to the Data Safety Monitoring Committee (DSMC) via the Clinical Research Safety Officer (CRSO), as well as the appropriate federal regulatory authority, following established guidelines. Reports to DSMC will be sent to the CRSO, entered into OnCore and communicated to the DSMC in a timely manner. Only Grade 4 and 5 events that are unexpected, with at least possible attribution to <sup>68</sup>Ga-DOTATOC PET, will require

an *expedited* report. The investigator will continue to follow or obtain documentation until the resolution of such an event.

Adverse events may also require reporting to the IRB per HSO-established guidelines.

### **Expedited Adverse Event Reporting**

Only Grade 4 and 5 events that are unexpected with at least "possible" attribution to the <sup>68</sup>Ga-DOTATOC PET will require an expedited report to the CRSO/DSMC (24-hour notification followed by complete report within 5 calendar days). All expedited adverse event reports will be reviewed by the DSMC.

For information about Adverse Event reporting to the CRSO/DSMC, refer to Data and Safety Monitoring Plan for this study (Appendix II).

### **Study Withdrawal/Discontinuation**

This is a low risk imaging protocol; the amount of physiologically active peptide is below physiological effects level and the radiation dose is below allowable levels. No adverse events are expected. Adverse events are recorded on the CRF at the following times:

after injection of radiopharmaceutical and before discharge from the PET Center following imaging during phone call 18-24 hrs after PET/CT

At any time, subjects may withdraw from the study (i.e., withdraw consent to participate) at their own request. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment. No disadvantage will arise for any subject who withdraws consent for participation at any time or who is withdrawn from the study by the Investigator. Reasons for discontinuation of study treatment will be recorded on the appropriate page of the CRF in any case and may include the following:

- Subject's request for withdrawal
- Investigator's decision that discontinuation is in the best interest of the subject
- Non-compliance with the regimen and timing that might result in dropping out from the study
- Development of an intolerable AE due to study participation as determined by the Investigator, subject, or both.
- Development of an intercurrent illness, condition, or procedural complication, which would interfere with the subject's continued participation.
- Subject is lost to follow-up.

Subjects who discontinue treatment will be asked to complete a follow-up examination prior to leaving the study, if possible. Any subject who discontinues treatment for medical reasons, e.g. because of adverse events (AEs) or clinical laboratory abnormalities, should be followed up at medically appropriate intervals in order to evaluate the course and to ensure reversibility or stabilization of the abnormality or event. If a subject fails to return for a scheduled visit, a documented effort must be made to determine the reason. This information should be recorded in the study records.

### **Privacy/Confidentiality Issues**

All routine medical data will be entered into the patient's electronic medical record. These records are only available to those with direct clinical duties to the patient. For all other records, the Principal investigator will collect data and enter it into password protected computer in a locked office. Each patient will have a unique identifier number, with the key to the patient's medical record number kept in a locked cabinet in the office. Only research associates or those individuals directly involved with the study will have access to data. Information is for research purposes only and when used for publication purposes,

all participants will have their names concealed. Access to identified patient information will be limited to the investigators listed within the IRB application. De-identified information with HIPAA identifiers removed will be available to other investigators following IRB approval. Confidentiality and security will be maintained for the database.

The database is stored behind a firewall (in addition to the institutional firewall) with the highest level of protection, i.e. the same level of protection as the on-line hospital information systems at the University of Iowa Hospitals. This means that users must logon to a web server that sits between the institutional firewall and the firewall to the database, and only this application server is allowed to query the database. Only users approved through our institutional review boards will be allowed access to patient identifiers. Other levels of authorization may exist for future approved users following IRB approval, e.g. access to de-identified data.

Data is initially collected in the medical record for each individual study participant. The information will be extracted from the patient's medical record and then transferred into the Case Report Form (CRF). The study data will be kept on site and in a securely locked room to protect patient confidentiality. The CRFs do not include personal identifiers for any participant. Numbers and initials are assigned for each participant and these become the identifying information for each study participant. A master list is kept separately that identifies which names go with which numbers and initials. Study personnel (PI and co-investigators) and government regulatory agencies have access to all research records as required by law. Others (such as law enforcement agencies) may have access to records as defined by law.

#### **Record Retention**

The PI must retain all study records by the applicable regulations in a secure and safe facility. The institution must consult with the PI before disposal of any study records, and must notify the PI of any change in the location, disposition or custody of the study files. The PI/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements. Records and documents pertaining to the conduct of this study, including Case Report Forms (Appendix IV), source documents, consent forms, laboratory test results, and medication inventory records, must be retained by the investigator for at least 2 years following submission of a New Drug Application. No study records will be destroyed without prior authorization from the Principal Investigator.

#### **4. Chemistry, Manufacturing, and Control**

The University of Iowa PET Center Radiopharmaceutical Laboratory maintains an environment that is adherent to USP <823>. Reagents used for the preparation of <sup>68</sup>Ga-DOTATOC are received and inspected per specification sheets and accepted or rejected. Accepted reagents are labeled with appropriate expiration dates, initialed, assigned identification numbers and quarantined in specified locations in the radiopharmaceutical laboratory. The University of Iowa (UI) PET Center Radiopharmaceutical Laboratory is staffed with expert radiochemists who oversee the preparation of the radiopharmaceuticals and are experienced in the compounding of the proposed investigational radiopharmaceutical because of its ongoing use under IND # 114,398.

Because Ga-68 has a 68 minute half life, production of <sup>68</sup>Ga-DOTATOC requires the use of a Germanium-68 (Ge-68) to Ga-68 generator. The eluted Ga-68 is purified following elution using an ion-exchange column prior to introduction into the radiolabeling vessel with DOTATOC to remove zinc-68 (the decay product of Ga-68), which builds up in the generator with the decay of Ga-68<sup>18</sup>.

According to the <sup>68</sup>Ga-DOTATOC Batch Record, the generator is connected to the ModularLab PharmTracer module and eluted with 0.1 N HCl directly to an ion exchange column for purification of the Ga-68 from Zn-68 (daughter nuclide of Ga-68 decay). The system includes a disposable GMP-certified

(sterile, pyrogen-free) “kit” that is snapped in place and manages (via software) the flow of reagents for purification, radiolabeling, and transfer of the final product to the product vial via sterilizing (0.22 µm filter). A new kit is used for each preparation and preparations are usually used for a single patient study. At the end of the process, the generator line is disconnected, capped, and the generator stands ready for connection to a new kit for a new preparation<sup>19</sup>.

The system then elutes Ga-68 with acetone/0.02 N HCl solution directly to a reaction vessel containing 40 micrograms of DOTATOC (obtained commercially) dissolved in 2 mL of sodium acetate buffer (pH 4). The solution is heated to 95 °C for 7 minutes at which time the heating element is turned off and the vessel is cooled with the addition of 2 mL isotonic saline for injection. Acetone is removed by distillation during the radiolabeling process and a test for residual is included in subsequent quality control prior to release<sup>20,21</sup>.

The solution is passed over a disposable C-18 cartridge, which retains [Ga-68]DOTATOC, while allowing any remaining free Ga-68 to pass. The cartridge is rinsed with isotonic saline for injection to remove any residual free Ga-68, followed by elution of <sup>68</sup>Ga-DOTATOC with 1 mL 47.5% ethanol in isotonic saline for injection directly through a sterile 0.22 micron membrane filter into the final collection vial<sup>22</sup>.

A 0.8 mL aliquot is then taken for quality control testing and the product line and vent filter are removed. Radiochemical yields of approximately 55% (uncorrected for decay) are routinely achieved using this process. The filter is retained for a QC pressure test to ensure filter integrity for sterilization. The production process can be conducted by a single person and requires approximately 1 hr to complete. Quality control procedures are usually carried out by two persons to expedite delivery of the final product vial for human use when QC parameter testing has been completed. The QC process takes approximately 20 minutes. The quality control tests are performed and compared to release criteria prior to release of the final product as shown in Table 2.

<b>Table 2. Analytical Specifications</b>	
<b>Test</b>	<b>Release Criteria</b>
Appearance	Clear and no visible impurities
Filter Test	2 bar for 1 minute
pH	3.0 – 7.0
Radiochemical	>90%
Endotoxins	<17.5 EU per mL
Acetone	<5000 ppm
Ethanol	<10%
Radionuclidic	Half life +/- 90 seconds

**Filter Test:** A filter pressure test is conducted by applying pressure to the sterilizing filter at 2 bar inert gas (nitrogen or argon) for 1 minute to ensure the integrity of the filter for sterilization.

**Bacterial Endotoxins:** Bacterial endotoxin test following a 50:1 dilution. Endotoxin/Limulus Amebocyte Lysate (LAL) testing using Endosafe-PTS Cartridges or alternative gel-clot vials as backup.

**pH:** The pH of final product should fall within the limits of 4.0-7.0 and is measured by spotting pH paper.

**Radiochemical Purity:** The system utilizes ITLC-SG media and 0.2 M Citric acid: ethanol (90:10) as the solvent. When using this TLC system, colloidal Ga-68, <sup>68</sup>Ga-DOTATOC, and free Ga-68 can be differentiated at *r<sub>f</sub>* – 0.0, 0.5 and 1.0, respectively.



**Sterility:** Following release, Tryptic Soy Broth (TSB) and Fluid Thioglycollate Media (FTM) are inoculated, incubated (TSB at room temp, FTM at 36 C) and checked for growth during the following 14 days. At the completion of the sterility test, the batch record is completed and filed.

**Acetone:** When acetone is used in the purification process, a gas chromatography test is used for analytical specification.

**Ethanol:** When ethanol is used in the purification process, a gas chromatography test is used for analytical specification.

**Radionuclidic Purity:** Half life measurement is determined by continuous measurement of radioactivity signal over 5 minutes and evaluation of the slope of the decay curve. The half life specification is obtained from Evaluated Nuclear Structure Data File (ENSDF) at the National Nuclear Data Center (NNDC) which can be accessed at [www.nndc.gov](http://www.nndc.gov). Additional standard operating procedures include out of specification investigations and reprocessing in the event of a 0.22 micron filter failure.

## 5. Labeling

Each unit dose will be made at the time of use due to the 68 minute half-life of the <sup>68</sup>Ga radiopharmaceutical, and labeled with the patient's name and ID in accordance with the usual and customary practice of radiopharmacy at the University of Iowa PET Center. The standard label includes patient name, medical identification number, time/date of completion of compounding, and identity of the radiopharmaceutical; all necessary information will be available.

The amount of radioactivity injected into the patient's IV will be recorded immediately prior to injection, with residual activity in the syringe recorded immediately after injection. The dose calibrators used in the University of Iowa are regularly maintained and calibrated in accordance with current NRC standards. An investigational record will be maintained with a copy of each drug label, also documenting time of injection, pre- and post-injection activity, time and date of injection, and patient identification information. Investigational radiopharmaceutical QA/QC information will be maintained for each unit dose for at least six years after the closure of this study. These data will provide important information should there be need to perform a rootcause analysis for a failure-to-perform of a given investigational PET/CT scan.

## 6. Pharmacology and Toxicology Information

The below summary of human experience provides strong evidence that the amount of investigational drug (DOTATOC) in mass quantity and the amount of radiation (as also provided via our measured radiation dosimetry) are acceptable in terms of risk. The NOAEL level of DOTATOC has never been established in humans, despite some of the below studies reporting much larger mass quantity use than we propose, with some using multiple large doses<sup>5</sup>. The radiation toxicity from the investigational radioisotope is also, accordingly, within the acceptable range for patients with life-threatening malignancies whose treatment we believe will benefit from the use of the proposed investigational imaging procedure. Accordingly, we believe the risk/benefit of our proposed investigation to be justified.

## 7. Previous Human Experience

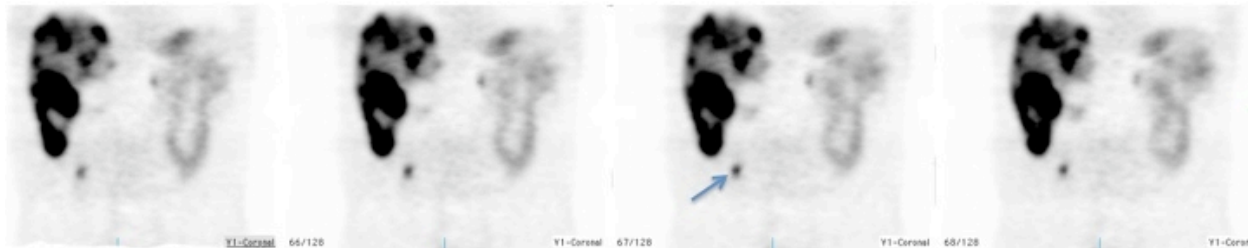
### Experience at the University of Iowa

Although there is extensive use of <sup>68</sup>Ga-DOTATOC PET/CT in Europe, the limited US experience is outlined here. The University of Iowa Radioactive Drug Research Committee and Institutional Review Board approved a study entitled "Biodistribution and Reproducibility of Ga-68 DOTATOC Positron Emission Tomography in Patients with Somatostatin Receptor Positive Tumors: A Feasibility Study"<sup>16</sup> (Appendix III). Subjects received two [<sup>68</sup>Ga]-DOTATOC PET/CT scans within 36 hours on each of five subjects who were selected based on biopsy proven NET with a positive Octreoscan™ within the past 3 months. <sup>68</sup>Ga-DOTATOC was prepared with GMP grade DOTATOC from Molecular Insight

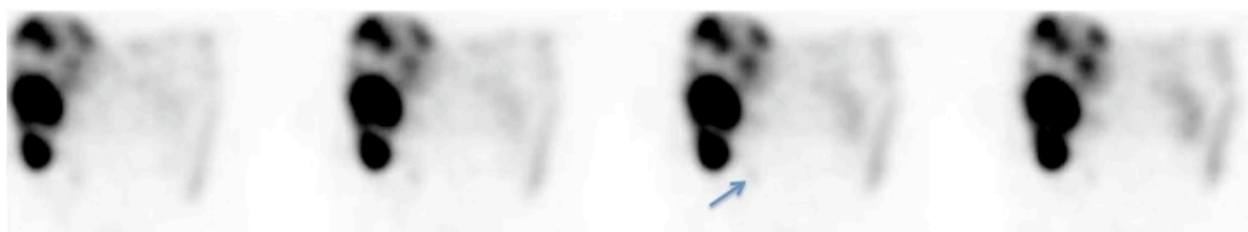
Pharmaceuticals using the Eckert-Zeigler ModularLab PharmTracer system. A comparison study is shown in **Figure 3**; the number of lesions is clearly greater with <sup>68</sup>Ga-DOTATOC PET compared to Octreoscan.

Biodistribution and reproducibility for these five subjects is summarized in **Fig 4 & Table 3**.

Ga-68 DOTATOC



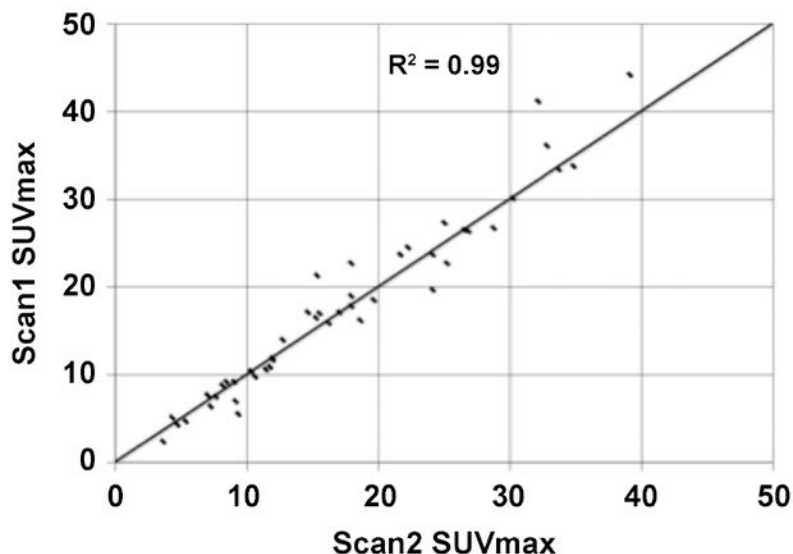
In-111 DTPA Octreotide



**Figure 3.** <sup>68</sup>Ga-DOTATOC PET/CT in patient with biomarkers and liver mets suggestive of ileal NET, but primary not seen on either high-resolution, contrast CT or Octreoscan. Arrows indicate ileal lesion clearly demonstrated on PET/CT with [<sup>68</sup>Ga]-DOTATOC that was (in retrospect) faintly visible on Octreoscan. Unknown primary lesion in ileum confirmed by surgical exploration. Also note addition liver lesions seen on <sup>68</sup>Ga-DOTATOC PET/CT.

**Table 3. SUV<sub>max</sub> reproducibility of <sup>68</sup>Ga-DOTATOC PET lesions in patients with metastatic NETs**

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Total
Organs Involved	Pancreas, bone, LN, peritoneum	Lung, bone, LN, liver	Heart, liver, LN	Bone, liver, LN	Lung, bone, LN, liver, sm bowel	
% Error * 5 target lesions	7.6 ± 7.3	11.8 ± 9.9	11.8 ± 7.8	4.6 ± 4.0	9.2 ± 5.9	9.0 ± 7.1
% Error * 10 target lesions	10.4 ± 10.4	15.7 ± 16.3	7.4 ± 7.4	5.0 ± 3.9	10.7 ± 6.2	9.8 ± 10.1
To evaluate the reproducibility of measurement of uptake of <sup>68</sup> Ga-DOTATOC, 5 patients with metastatic NET underwent two DOTATOC PET scans. Standardized uptake values (SUV <sub>max</sub> ) were measured for 5 target lesions (max 2 per organ) and 10 target lesions (max 5 per organ) per subject. Target lesions included representative lesions from all involved organs and the lesions with the highest activity for each organ. Percentage error (i.e. reproducibility) was calculated for each lesion as <b>Percentage Error = 100*ABS (Scan 2-Scan 1)/((Scan 2 + Scan 1)/2)</b> <sup>23</sup> . *mean ± standard deviation						



**Figure 4.** Reproducibility of <sup>68</sup>Ga-DOTATOC PET in patients with NET. Results for each subject and all target lesions in Table 2 are shown. The average (mean ± SD) reproducibility was 10% ±10% for 50 target lesions. The scatter graph (excluding 2 lesions with SUV>50 for display purposes) shows the high correlation of SUVmax of all target lesions on Scan 1 and 2 (R<sup>2</sup>=0.99).

Production of <sup>68</sup>Ga-DOTATOC at University of Iowa

The cGMP grade DOTATOC was purchased from Bachem with the written permission of Molecular Insight Pharmaceuticals, Inc. Radiolabeling was performed using a TiO<sub>2</sub> germanium-gallium generator and automated ModularLab PharmTracer, both from Eckert-Zeigler Eurotope GmbH. This system utilizes a sterile cassette that is replaced for each radiolabeling procedure. Performance has been very reproducible with radiochemical, radionuclidic, sterility as shown in Table 4.

Table 4. Performance of [ <sup>68</sup> Ga]DOTATOC prepared using automated cassette-based system.				
Parameter	Test Method	Specification	Result±SD (n = 17)	% Pass
Radiochemical Purity (%)	ITLC*	> 90%	98%±1%	100
Specific Activity (MBq nmole <sup>-1</sup> )	Dose Calibrator	20 MBq nmole <sup>-1</sup>	31±4	100
Acetone (ppm)	Gas Chromatography	< 5000 ppm <sup>a</sup>	399±64	100
Ethanol (%)	Gas Chromatography	< 10%	5±0	100
Endotoxins EU mL <sup>-1</sup>	Limulus Amebocyte Lysate	< 175 EU <sup>§</sup> mL <sup>-1</sup>	Pass	100
Sterility	Fluid Thioglycolate Soybean Casein	No Turbidity 14 days	Pass	100
pH	pH paper	4.5-8.5	6±1	100
Filter Pressure Test	Automated N <sub>2</sub> Stream	2 bar	Pass	100

European Experience in Humans

The potential of <sup>68</sup>Ga-DOTATOC PET/CT for improved imaging of somatostatin receptor positive tumors has been recognized since early comparative studies noted improvements in detection sensitivity and image quality in comparison to [<sup>111</sup>In]DTPA-octreotide SPECT<sup>24</sup>. Although we have successfully employed [<sup>111</sup>In]DTPA-octreotide SPECT/CT (Octreoscan™) + a diagnostic CT for diagnosis, staging, and monitoring of NET in children and adults<sup>2,25</sup>, our RDRC approved studies (**Figures 3 and 4**) as well as comparisons of <sup>68</sup>Ga-DOTATOC and Octreoscan™ by European investigators, support our hypothesis that <sup>68</sup>Ga-DOTATOC will provide at least equivalent, and likely objective improvements in, diagnosis and staging of neuroendocrine tumors and other somatostatin receptor positive tumors<sup>26-28</sup>. Several advantages of <sup>68</sup>Ga-DOTATOC PET/CT have been pointed out through these published studies. For example, Gabriel

and colleagues concluded that <sup>68</sup>Ga-DOTATOC PET/CT shows a significantly higher detection rate (higher sensitivity) compared to conventional Octreoscan™ SPECT/CT based on a randomized prospective study. These findings are corroborated by a prospective study concluding that <sup>68</sup>Ga-DOTATOC PET was superior to Octreoscan™ in detection of metastases in the lung, skeleton, liver, and brain<sup>15</sup>. A study demonstrating that <sup>68</sup>Ga-DOTATOC PET influences patient management in ≥ 33% of patients further supports the introduction of this imaging technique into the United States<sup>29</sup>.

Comparisons of <sup>68</sup>Ga-DOTATOC and Octreoscan by European investigators, support our early observations that <sup>68</sup>Ga-DOTATOC will provide at least equivalent, and likely objective improvements in, diagnosis and staging of NETs<sup>26-28</sup>. Several advantages of <sup>68</sup>Ga-DOTATOC PET/CT have been pointed out through these published studies. For example, Gabriel and colleagues concluded that <sup>68</sup>Ga-DOTATOC PET/CT shows a significantly higher detection rate (higher sensitivity) compared to conventional Octreoscan SPECT/CT based on a randomized prospective study. These findings are corroborated by a prospective study concluding that <sup>68</sup>Ga-DOTATOC PET was superior to Octreoscan in detection of NET metastases in the lung, skeleton, liver, and brain<sup>15</sup>. A study demonstrating that <sup>68</sup>Ga-DOTATOC PET influences patient management in ≥ 33% of patients further supports our proposed research<sup>29</sup>.

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## Appendix II: Data and Safety Monitoring Plan

### HCCC Clinical Trial Data and Safety Monitoring Plan (DSMP)

**Date:** 2/24/15

**IRB#:** 20122736 IND# 114,398

**Study Title:** Comparator Study of <sup>68</sup>Ga-DOTATOC PET/CT with Octreoscan + high-resolution, contrast-enhanced CT for diagnosis and staging in neuroendocrine tumors and other somatostatin receptor positive tumors

**Principal Investigator:** M. Sue O'Dorisio, MD, PhD

**Co-Investigators:** Yusuf Menda, MD, Thomas ODorisio, MD, Joseph Dillon, MD, Blanca Schafer, MS, and Mary Schall, BSN

All investigator-initiated protocols will be subject to ongoing monitoring of accrual, subject eligibility, protocol modifications and continuing reviews.

#### Type of Clinical Trial (check all that apply):

Investigator-initiated (Iowa)

Investigator-initiated, multi-center (non-Iowa)

- Is this study monitored by an outside DSMB? Yes  No

Compassionate-use drug protocol

Pilot study

Phase I

Phase I/II

Phase II

Phase III

Phase IV

**Study risk-level (refer to attached risk-level assessment for this study):**

- \_\_\_\_\_ **Level 1**—low risk of morbidity or death, \* <<1% of death or any adverse event
- X** **Imaging Study Level 2**—risk of death\* <1% or any adverse event 1% – 5%
- \_\_\_\_\_ **Level 3**—risk of death\* 1% – 5% or grade 4 – 5 SAE 1% – 5%
- \_\_\_\_\_ **Level 4**—risk of death\* >5% or grade 4 – 5 SAE >15%
- \_\_\_\_\_ Drugs being used on a “compassionate” basis

\* *Risk of death” refers specifically to 100-day treatment-related mortality*

**Risk Level 2**

Interventional trials with a risk of death\* <1% or any adverse event 1% – 5%, i.e. behavioral interventions, nutritional therapies, low risk procedures (e.g., endoscopy, glucose-tolerance tests, induced sputum, skin or muscle biopsy, nasal wash, lumbar puncture, bone marrow biopsy, imaging requiring sedation), as well as therapeutic trials involving agents with known safety profiles already licensed for the indication and age group. Most disease-prevention trials will be considered at least a Risk Level 2.

Study Safety Review: The PI or designated study personnel will review all data, including completeness of study data, enrollment, protocol deviations, drop-outs, adverse events on a regular basis and provide an annual report to the DSMC and PRMC.

- Subject accrual data will be obtained from OnCore on an ongoing basis by the CTRM during accrual review for the PRMC.
- The research coordinator or data manager for the study will register new subjects in OnCore.
- Adverse events will be reported to the CRSO as defined in the DSMP for the study
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the PI, DSMC Chair/acting Chair, CRSO, and CTRM. Tables I below provide CRSO reporting guidelines.

*Routine Adverse Event Reporting*

The clinical research coordinator is responsible for collecting and recording all clinical data. As these results are collected, all toxicities and adverse events will be identified and reported to the principal investigator. The principal investigator will determine relationship of the event to the study drug and decide course of action for the study participant. The PI or designated study personnel will review all data, including completeness of study data, enrollment, protocol deviations, drop-outs, adverse events on a regular basis and provide an annual report to the DSMC and PRMC.

The CRSO will be responsible for collecting and collating the appropriate data provided by the PI for the DSMC. As part of the ongoing monitoring of this study, the PI will maintain an AE summary table and a protocol deviation log.

Routine reporting of adverse events for PI-initiated trials to the DSMC via the CRSO is described in Table 1:



**Table I: Routine Reporting of Adverse Events for PI-initiated Trials**

Attribution	Adverse Event				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Not required	Not required	Not required	Not required	CRSO
Unlikely	Not required	Not required	Not required	Not required	CRSO
Possible	CRSO	CRSO	CRSO	CRSO	CRSO
Probable	CRSO	CRSO	CRSO	CRSO	CRSO
Definite	CRSO	CRSO	CRSO	CRSO	CRSO

**Table II: Expedited Adverse Event Reporting**

*IND Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention.*

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)		
<p><b>NOTE: Investigators <u>MUST</u> immediately report to the sponsor <u>ANY</u> Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)</b></p> <p><b>An adverse event is considered serious if it results in <u>ANY</u> of the following outcomes:</b></p> <ol style="list-style-type: none"> <li>1) Death</li> <li>2) A life-threatening adverse event</li> <li>3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours</li> <li>4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions</li> <li>5) A congenital anomaly/birth defect.</li> <li>6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).</li> </ol>		
<p><b><u>ALL SERIOUS</u> adverse events that meet the above criteria <u>MUST</u> be immediately reported to the sponsor within the timeframes detailed in the table below.</b></p>		
Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Time frames
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) Part of the CAEPR.

**Expedited AE reporting timelines are defined as:**

- o "24-Hour; 5 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- o "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

<sup>1</sup> Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

**NOTE:** Deaths clearly due to progressive disease should **NOT** be reported expeditiously but rather should be reported via routine reporting methods.

\*\* For Hospitalization Only — Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for Phase of study, expected or unexpected and attribution.

## Eligibility

### Inclusion Criteria:

- Signed informed consent.
- Age  $\geq$  2 years.
- Biopsy proven neuroendocrine tumor, neuroblastoma, medulloblastoma, or other somatostatin receptor positive tumor.
- Off Sandostatin-LAR >4 weeks and off immediate release (subcutaneous) for 12 hrs prior to <sup>68</sup>Ga-DOTATOC PET-CT.
- Karnofsky performance status or Lansky Play Scale status of  $\geq$  50 (or ECOG/WHO equivalent).
- Subject is male; or is a female who is either pre-menarchal, surgically sterile (has had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (> 1 years without menses), non-lactating, or of childbearing potential for whom a serum pregnancy test (with the results known prior to investigational product administration) is negative. A negative serum pregnancy test will be required for all female subjects with child bearing potential. If a false pregnancy test is suspected, e.g., perimenopausal condition, an obstetrician will be consulted to determine if she is/is capable of becoming pregnant.
- No therapy other than Sandostatin since last Octreoscan + diagnostic CT;
- Fresh frozen (recommended) or paraffin fixed (required) specimen of primary or metastases available for RNA and IHC;

### Exclusion Criteria:

- Pregnancy or breast feeding
- Surgical resection, chemotherapy, radiation therapy, or biologic therapy since last Octreoscan + CT. Continuation of the same dose of Sandostatin-LAR or subcutaneous Sandostatin is allowed.
- Medical condition uncontrolled by treatment making completion of study unlikely.
- Weight more than 400 pounds (Subjects who weigh more than 400 pounds will not be able to fit inside the imaging machines).
- Inability to lie still for the entire imaging time (e.g. cough, severe arthritis, etc.)
- Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc.)
- Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance

## Stopping Rules

### Study Withdrawal/Discontinuation

This is a low risk imaging protocol; the amount of physiologically active peptide is below physiological effects level and the radiation dose is below allowable levels. No adverse events are expected. Adverse events are recorded on the CRF at the following times:

immediately following the PET/CT

at the conclusion of a 2 hrs observation time from time of injection of radiopharmaceutical  
during phone call 18-24 hrs after PET/CT

Within one week following PET/CT at outpatient visit with blood tests

At any time, subjects may withdraw from the study (i.e., withdraw consent to participate) at their own request. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment. No disadvantage will arise for any subject who withdraws consent for participation at any time or who is withdrawn from the study by the Investigator. Reasons for discontinuation of study treatment will be recorded on the appropriate page of the CRF in any case and may include the following:

- Subject's request for withdrawal
- Investigator's decision that discontinuation is in the best interest of the subject
- Non-compliance with the regimen and timing that might result in dropping out from the study
- Development of an intolerable AE due to study participation as determined by the Investigator, subject, or both.
- Development of an intercurrent illness, condition, or procedural complication, which would interfere with the subject's continued participation.
- Subject is lost to follow-up.

Subjects who discontinue treatment will be asked to complete a follow-up examination prior to leaving the study, if possible. Any subject who discontinues treatment for medical reasons, e.g. because of adverse events (AEs) or clinical laboratory abnormalities, should be followed up at medically appropriate intervals in order to evaluate the course and to ensure reversibility or stabilization of the abnormality or event. If a subject fails to return for a scheduled visit, a documented effort must be made to determine the reason.

This information should be recorded in the study records.

## **Toxicities**

### **Pharmacology and Toxicology Information**

The below summary of human experience provides strong evidence that the amount of investigational drug (DOTATOC) in mass quantity and the amount of radiation (as also provided via our measured radiation dosimetry) are acceptable in terms of risk. The NOAEL level of DOTATOC has never been established in humans, despite some of the below studies reporting much larger mass quantity use than we propose, with some using multiple large doses<sup>5</sup>. The radiation toxicity from the investigational radioisotope is also, accordingly, within the acceptable range for patients with life-threatening malignancies whose treatment we believe will benefit from the use of the proposed investigational imaging procedure. Accordingly, we believe the risk/benefit of our proposed investigation to be justified.

### **Radiation Risk**

The maximum amount of radiation from the research-related radiation procedures in this study is equivalent to approximately 60 % of the annual radiation limit for a medical worker. This does not include the radiation you received with your last Octreoscan and high-resolution, contrast-enhanced CT. Although there are no proven harmful effects from this amount of radiation, long term effects on your health such as cancer cannot be ruled out with certainty. This dose estimate takes into account only the exposure to research procedures in this project. If you have participated in other research studies involving radiation exposure, you should be aware that the risk of effects from radiation is believed to increase with each exposure you receive, including studies performed as part of your medical care.

### **PET Scan Risk**

The PET/CT scanner is a large machine with a hollow tube, open on both ends, that which will be used to see how much <sup>68</sup>Ga-DOTATOC is taken into your tumor. You will be asked to lie on your back on a special table that slides into the tube. The sides of the tube will be fairly close to your body and you will be in this scanner for approximately 15-35 minutes. You will be able to talk to people in the room through a speaker system. We will monitor you closely while you are inside the scanner. The risks from the PET scan include the radiation described above, pain from lying still on the table or a panic attack if you have claustrophobia.

### **Women Capable of Becoming Pregnant**

If you are a woman who is capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to your fetus, or risks to your fetus that we did not anticipate, associated with being in the study. There may be long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. If you believe or know you have become pregnant while participating in this research study, please contact Dr. MS O'Dorisio at 319-356-3595 as soon as possible so that counseling can be provided to you.

### **Radiation Exposure in Women Who are Breast Feeding**

You may not participate in this study if you are breast feeding an infant. There is a chance that the <sup>68</sup>Ga-DOTATOC could travel to your infant in your breast milk and cause unknown risks to your child.