# Impact of Ga-68 DOTATOC PET/CT on Management of Somatostatin Receptor Positive Tumors

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**Project Goal**

Evaluate the impact of Ga-68 DOTATOC PET-CT on management of patients with somatostatin receptor positive tumors

## I. Introduction:

### Neuroendocrine 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 tumor. 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[1]. Among NETs, 25% have distant metastases and 25% have regional involvement at the time of initial diagnosis[1].

Surgery is the only curative option for NETs; however, curative surgery in malignant NET is possible in less than 30% of patients. 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[2]. Chemotherapy is generally not effective in low grade NETs, but it may be helpful in high grade and pancreatic NETs. Other specific therapies in NETs are the mTOR-inhibitor everolimus, which in combination with octreotide has been shown to improve progression free survival by approximately 6 months in pancreatic NETs[3]. The tyrosine kinase inhibitor sunitinib has also demonstrated significant antitumor efficacy in pancreatic NETs[4].

### Conventional Imaging of Neuroendocrine Tumors

The radiological detection and staging of neuroendocrine tumors is challenging and requires a multimodality approach. CT is usually the initial imaging modality in staging and restaging of neuroendocrine tumors. The performance of CT in detection of NET is variable depending on the location; the sensitivity also drops significantly in lesions smaller than 1cm[5]. MRI may be more sensitive than CT for liver and bone marrow metastases, but small nodal metastases may be missed on both imaging modalities[6].

The standard nuclear medicine technique for imaging NET is somatostatin receptor scintigraphy with In-111 Octreotide (OctreoScan®), which primarily targets the somatostatin receptor subtype 2 (sstr2) on NET (Figure 1). The sensitivity of In-111 Octreotide is >90% for well-differentiated carcinoid tumors and majority of pancreatic NETs, but is lower for NETs with weaker expression of sstr2 such as insulinoma [7]. The sensitivity of OctreoScan is lower for small tumors less than 1 cm due to the resolution limits of SPECT (Single Photon Emission Computerized Tomography) imaging and may be also limited in detection of liver metastases due to high background hepatic uptake[8].

### Somatostatin Receptor PET Imaging with $^{68}$Ga-DOTA$^{0}$-Tyr$^{3}$-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. A number of Ga-68 DOTA-conjugated peptides have been introduced, including $^{68}$Ga-DOTA$^{0}$-Tyr$^{3}$-octreotide ($^{68}$**Ga-DOTATOC**), $^{68}$Ga-DOTA$^{0}$-1Nal$^{3}$-octreotide ($^{68}$Ga-DOTANOC) and $^{68}$Ga-DOTA$^{0}$-Tyr$^{3}$-octreotate ($^{68}$Ga-DOTATATE) (Figure 2). All of these radiolabeled peptides bind to sstr2, although DOTANOC also binds to sstr3 and sstr5, and DOTATOC to sstr5[9]. The advantages of Ga-68 based somatostatin receptor PET imaging over OctreoScan SPECT involve the higher imaging resolution, the higher affinity of the radiopeptide for the sstr2 and the accurate quantitation of uptake due to robust attenuation correction. $^{68}$Ga- DOTATOC has been found to be superior to OctreoScan in detection of skeletal and pulmonary involvement of neuroendocrine tumors[10].

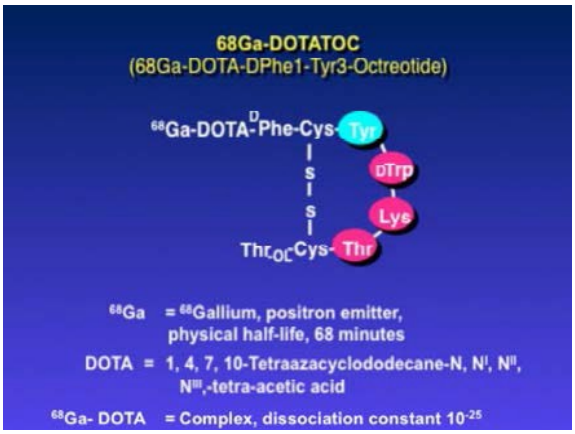


**Figure 1** Chemical identity of [$^{68}$Ga]DOTATOC IND # 114,398

## II. Rationale and overall study design

### Rationale:

$^{68}$Ga-DOTATOC positron emission tomography (PET) is not approved for use in the United States. IND #114,398 is currently active under the above named investigators for imaging with Ga-68 DOTATOC PET and IND #61,907 is active for treatment with $^{90}$Y-DOTATOC PRRT in somatostatin receptor positive tumors. We have conducted a single institution Phase II trial of safety and efficacy of $^{68}$Ga-DOTATOC PET in neuroendocrine tumors (see "Previous use in Humans").

The purpose of this protocol is to evaluate the impact of $^{68}$Ga-DOTATOC PET/CT imaging on management of patients with somatostatin receptor positive tumors. $^{68}$Ga-DOTATOC PET/CT would replace $^{111}$In-DTPA-Octreotide single photon emission tomography (SPECT/CT) imaging in view of its significant advantages: (1) $^{68}$Ga-DOTATOC has a higher affinity for somatostatin receptors (sstr2) compared to Octreoscan™ [11]; (2) The radiation dose from $^{68}$Ga-DOTATOC is significantly lower compared to In-111 Octreotide, 3.4 mSv versus 12 mSv for standard administered doses[12]; (3) [$^{68}$Ga]DOTATOC PET/CT can be completed within 2 hours compared to an Octreoscan™ which requires 3 visits over 24 hours, making $^{68}$Ga-DOTATOC a much more convenient imaging choice for patients.

### Overall Study Goal and Study Design

**Project Goal**
This study is planned to evaluate the impact of $^{68}$Ga-DOTATOC PET/CT imaging on management of patients with somatostatin receptor positive tumors.

### Project Design

This is a prospective, Phase II, single center, open-label study in a total of 200 subjects with histologically proven neuroendocrine tumor or other somatostatin receptor positive tumors. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive $^{68}$Ga-DOTATOC and undergo a PET/CT imaging study. Subjects may receive a second $^{68}$Ga-DOTATOC PET/CT for suspected disease progression, for restaging prior to institution of new therapy, or for measurement of disease response after therapy. This second scan may be obtained at any time from 6-36 months following the first scan.

**Participant Enrollment**
Participants will be recruited from the Neuroendocrine Tumor Clinics at the University of Iowa Comprehensive Cancer Center Clinics and the University of Iowa Children's Hospital. Participants may also request to join the study via clinicaltrials.gov.

**Schema**

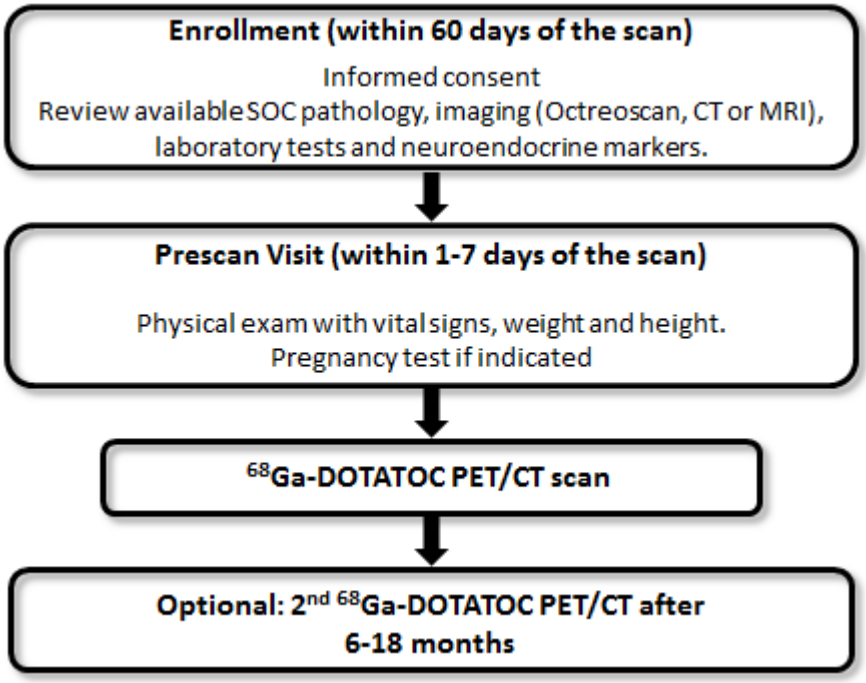


**Figure 2** Study Schema

**III. Clinical Protocol**
**Inclusion Criteria:**

1. Age ≥ 6 months.
2. Histologically diagnosed or suspected (pediatric only) neuroendocrine tumor or other tumor with probable somatostatin receptors subtype 2
3. Karnofsky performance status or Lansky Play Scale status of ≥ 60 (or ECOG/WHO equivalent).
4. Subject is male; or is a female who is either surgically sterile (has had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (>1 years without menses), ≥60 years old,, or of childbearing potential for whom a pregnancy test (with the results known prior to investigational product administration) is negative. A negative 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 not capable of becoming pregnant. Female must also be non-lactating.

**Exclusion Criteria**

5. Subject weighs more than 450 pounds (Subjects who weigh more than 450 pounds will not be able to fit inside the imaging machines) or otherwise cannot be safely fit into the imaging system.
6. Inability to lie still for the entire imaging time (e.g. cough, severe arthritis, etc.)
7. Inability to complete the needed investigational and standard-of-care imaging examinations due to

other reasons (severe claustrophobia, radiation phobia, etc.)

8. Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the investigator, may significantly interfere with study compliance.
9. Peptide receptor radionuclide therapy (PRRT) within 4 weeks of Ga-68 DOTATOC PET/CT scan
10. Treatment with Sandostatin LAR within 4 weeks, SQ Octreotide within 12 hours, or Lanreotide injection within 8 weeks of Ga-68 DOTATOC PET/CT (+/-5%)

**Procedures Informed**

**Consent**

Subjects who appear to meet 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 and the original consent will be placed in the patient's research folder.

**Physical Examination and Medical History**

Physical examination and medical history will be performed to ensure suitability according to the inclusion and exclusion criteria at screening (Visit 1) and adverse events will be collected at the time points specified in the Schedule of Events **(Table 1).**

**Table 1. Schedule of Study Events**

| | Visit 1[a] | Scan (Visit 2) | 1 Day (18-36hrs)[c] | 1-14 Days | 6-18 months[g] |
|---|---|---|---|---|---|
| Informed consent | X | | | | |
| Medical history | X | | | | |
| Physical examination | X | | | | X |
| Concomitant meds | X | | | | X |
| Blood pressure, temp, respiratory rate, heart rate, weight[d], height[d] | X | X | | | X |
| Pregnancy test (serum) | X[b] | X[f] | | | X[f] |
| $^{68}$Ga-DOTATOC PET/CT | | X | | | X |
| Pre-scan form[e] | X | | | | X |
| Post-scan form[e] | | | | X | X |
| Adverse events | | X | X | | X |

a- (-60 to 0 days) To facilitate scheduling, some screening procedures may occur up to 2 months prior to the first dose of study drug.
b- A serum pregnancy test
c- phone call
d- Height and weight at Visit 1. Values will be obtained from EPIC notes.
e- see form in Appendix II
f- A urine pregnancy test may be obtained if serum pregnancy test was obtained more than 24 hours prior to scan
g- A second PET scan will be offered to patients who undergo surgery/PRRT/targeted therapy/chemotherapy. This will comprise Visits 3, 4 and an additional phonecall. The requirements will be the same as visits 1, 2 and the follow up phonecall.

Events in Table 1 will be repeated (except for informed consent unless a new version is available) if patient is eligible for the optional second scan. Patients undergoing surgery, PRRT, targeted therapy or chemotherapy in response to the results of the first PET scan will be eligible for a second, follow up PET scan per their physician's recommendation. 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.

**Pregnancy Test**

Female subjects of childbearing potential will have a pregnancy test (serum or urine) 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 positive pregnancy test is suspected, e.g., perimenopausal condition, an obstetrician will be consulted to determine if she is/is capable of becoming pregnant.

**$^{68}$Ga-DOTATOC PET/CT Scan**

Study participants who complete Visit 1 and have been deemed eligible, will undergo the $^{68}$Ga-DOTATOC PET/CT. Subjects may be offered a medication (alprazolam or lorazepam) to help them relax. The injected dose for adults will be 3-4 mCi (target: 4 mCi +/- 10%) containing <50 µg $^{68}$Ga-DOTATOC and will be injected via IV access lines (peripheral or central lines are acceptable.). The dose for children will be 0.043 mCi/kg with a maximum dose of 3 mCi. A low tube current CT will be obtained for attenuation correction and localization of PET/CT data. If a diagnostic CT scan is also clinically indicated, this can be performed on the PET/CT system in the same imaging session. All investigational PET/CT scans will be read by a board-certified nuclear medicine physician with established expertise. A report will be generated for the site(s) of the primary tumor (if visible/present) and metastases, which will be entered into the patient's medical record. If contrast-enhanced CT scans are obtained, these will be interpreted by the subspecialty radiologist per clinical routine and entered into the chart.

**Investigational Radiopharmaceutical Administration**

$^{68}$Ga-DOTATOC will be administered intravenously in conjunction with the PET/CT scan. The one-time nominal injected dose will be 4mCi (+/- 10%) containing <50 µg $^{68}$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 pediatric 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.

$^{68}$Ga-DOTATOC is produced at the University of Iowa PET Imaging Center by qualified personnel following USP <823> standards. All quality control tests will be completed satisfactorily prior to final release of the drug product, with the exception of sterility testing (test takes two weeks for completion). Subjects will be observed and monitored in the PET/CT area until the scan is completed which is approximately for 90 min after the administration of $^{68}$Ga-DOTATOC (60 min uptake period before imaging starts and approximately 30 min imaging time). The subject or his/her guardian will be queried for constitutional symptoms suggesting an adverse reaction to the investigational radiopharmaceutical. These will be evaluated as a drug-related adverse reaction. Staff will release subjects from clinic as appropriate, based on query results. The following day, all subjects will be contacted by phone or seen in the clinic and again asked if untoward/adverse events occurred after release. 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.

**Data Analysis:**

The primary end-point of the study is the change in management of patients based on findings of the $^{68}$Ga-DOTATOC PET/CT scan. UIHC referring physicians will be asked to fill out pre-PET and post-PET scan forms (Appendix II) to provide information on the management and treatment strategy of the patient before the $^{68}$Ga-DOTATOC PET/CT and after the information from the $^{68}$Ga-DOTATOC PET/CT study is available. This is the same methodology used in the National Oncologic PET Registry study; change in management strategy criteria are modified for the specific treatment strategies used in NET (Table 2).

Table 2: Criteria for minor change, major change and no change in management strategies based on comparison of pre-PET and post-PET plans.

| | Pre-PET plan | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Post-PET plan** | **Watch** | **More Imaging** | **Octreotide LAR / Lanreotide** | **Tissue biopsy** | **Primary Debulking Surgery** | **PRRT** | **Chemotherapy OR Other Biological Modifiers** | **Liver Directed Therapy[2]** | **External beam radiotherapy** | **Supportive care** |
| Watch | No change | Minor | Major | Minor | Major | Major | Major | Major | Major | Minor |
| More imaging | Minor | No change | Major | Minor | Major | Major | Major | Major | Major | Minor |
| Octreotide LAR / Lanreotide | Major | Major | No Change | Major | Major | Major | Major | Major | Major | Major |
| Tissue biopsy | Major | Major | Major | No change | Major | Major | Major | Major | Major | Major |
| Primary Debulking Surgery | Major | Major | Major | Major | No change | Major | Major | Major | Major | Major |
| PRRT[3] | Major | Major | Major | Major | Major | No change | Major | Major | Major | Major |
| Chemotherapy or Other Biologic Modifiers[1] | Major | Major | Major | Major | Major | Major | No Change | Major | Major | |
| Liver Directed Therapy[2] | Major | Major | Major | Major | Major | Major | Major | No change | Major | Major |
| External beam radiotherapy | Major | Major | Major | Major | Major | Major | Major | Major | No change | Major |
| Supportive care | Minor | Minor | Major | Major | Major | Major | Major | Major | Major | No change |

1: mTOR inhibitors, tyrosine kinase inhibitors
2: Radiospheres, chemoembolization, liver transplant
3: Peptide Receptor Radionuclide Therapy

Subjects whose post-scan treatment plan represents a major change (whether or not the pre-scan treatment plan was a major change), will be presented at the Neuroendocrine Tumor Board, for a consensus recommendation regarding treatment. The minutes of this tumor board discussion and recommendation will be retained with the subject's study chart.

**Risks**

**Risks of Study Drug**

Research radiation dose estimate: Our calculations estimate that the effective whole-body dose of the $^{68}$Ga-DOTATOC PET/CT is approximately 1.6 rem, less than the radiation dose from a conventional $^{18}$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. 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 $^{68}$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, dosage infiltration, risks from IV access, and the inconvenience of the investigational PET/CT scan. If a subject elects to take medication to help them relax for the scan, they may experience drowsiness or unclear thinking. They will be instructed not to drive or operate machinery for 12-24 hours after receiving the medication. A driver will be required, if this type of medication is given the day of the 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**
**Adverse Event**
**1.** 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 adverse event. 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**

**1. 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. Subjects will report the type and severity of AEs without being given a list of fixed symptoms beforehand. The Investigator will determine the relationship of any AE to study drug (causality) and record it on the appropriate section of the AE CRF as well as the start date of the event, event grade, and whether or not the event meets one or more of the definitions of an SAE. 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.

**2. 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 or stabilization, even if this is after the study reporting period.

**Data and Safety Monitoring**
**See Appendix 1 for Data and Safety Monitoring Plan**

**Assessing Toxicity:**
Toxicity will be graded according to NCI's Common Toxicity Criteria (CTCAE v4). The principal investigator will 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:**

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. As part of the ongoing monitoring of this study, the PI will maintain an AE summary table to be reviewed during the quarterly audits.

**For Guidelines of Routine Adverse Event Reporting See Appendix 1**

**Study Withdrawal/Discontinuation**
This is a low risk imaging protocol; the amount of radioactive 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:

- at the conclusion of the PET/CT scan (approximately 90 min after the injection of the radiopharmaceutical)
- during phone call 18-36 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.
-

**Statistical Considerations**

This study will evaluate the impact of $^{68}$Ga-DOTATOC PET/CT imaging in the management of patients with neuroendocrine tumors and other somatostatin receptor positive tumors. Participants will be recruited from the Neuroendocrine Tumor Clinics at the University of Iowa Comprehensive Cancer Center Clinics and the University of Iowa Children's Hospital, and individuals may also request to join the study via clinicaltrials.gov. The study will be open-label and subjects with histologically proven neuroendocrine tumor or other somatostatin receptor positive tumors will be recruited. Subjects will

receive $^{68}$Ga-DOTATOC and undergo a PET/CT imaging study. The endpoint of the study will be the change in management of patients based on findings of the $^{68}$Ga-DOTATOC PET/CT scan. Three levels of change will be assessed: no change, minor change and major change based on findings after receiving $^{68}$Ga-DOTATOC and undergoing PET/CT. A previous pilot study of 70 patients (46 of which meet our current inclusion criteria), suggested that 37% of the population had experienced a major change in patient management following $^{68}$Ga-DOTATOC imaging. We operate under the assumption that a 49% major change in management within this population will be clinically relevant should $^{68}$Ga-DOTATOC induce clearer image prompting change.

A sample size of 180 patients achieves 90% power to detect a difference of 12% using a two-sided Z test (also a binomial exact test reaches similar power) when the null hypothesized proportion was used to estimate the standard deviation. The target significance is 0.05 and the actual significance level is 0.045. The results on power justification assume that the proportion of major change in patient management is 37% under the null. Note that we design the power around a two-sided alternative so we can gain more power for the one-sided (as our medical intuition seems to suggest.)

There is a potential for loss to follow-up or attrition within this population. We estimate this rate to be around 10%. In order to have 180 evaluable patients, our estimated sample size is 180 / (.90) = 200 subjects.

We will test the null hypothesis of 37% versus a clinically relevant alternative of 49% of major change in patient management. If the null is rejected at significance level of 0.05, we will have enough evidence to attribute our decision to $^{68}$Ga-DOTATOC effect.

Within each category of patient management change (No—Minor—Major), we will report the estimated proportion of subjects as well as 95% confidence intervals around these estimates.

**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 store this source data in a locked office. Each patient will have a unique identifier number( e.g. IMPACT001, IMPACT002) . A log of patient study ID's and Medical Record Numbers will be stored in our secured OnCore database. 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 or research record for each individual study participant. The information will be extracted from the patient's medical record and research 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. 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 III), 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.

**IV. 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 [$^{68}$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 that oversee the preparation of the radiopharmaceuticals and are experienced in the compounding of the proposed investigational radiopharmaceutical, having prepared over 200 patient doses of $^{68}$Ga-DOTATOC for phase I IND studies.

Because Ga-68 has a 68 minute half life, production of $^{68}$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.

According to the $^{68}$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) cassette 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 cassette is used for each preparation and preparations are used for one or two patient studies. 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.

The system then elutes Ga-68 with acetone/0.02 N HCl solution directly to a reaction vessel containing 50 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 acetone is included in subsequent quality control prior to release.

The solution is next passed over a disposable tC18 cartridge, which retains $^{68}$Ga-DOTATOC while allowing any remaining free Ga-68 to pass through. The cartridge is rinsed with isotonic saline for injection to remove any residual free Ga-68, followed by elution of $^{68}$Ga-DOTATOC with 1 mL of 47.5% ethanol in water directly through a sterile 0.22 micron filter and into the final collection vial.

A 0.8 mL aliquot is taken for quality control testing. Radiochemical yields of approximately 55% (uncorrected for decay) are routinely achieved using this process. The final sterilizing 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 people to expedite delivery. 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 3.

**Table 3. Analytical Specifications**

| Test | Release Criteria |
|---|---|
| Appearance | Clear and no visible impurities |
| Sterile Filter Test | 2 bar for 1 minute |
| pH | 4.0 – 7.0 |
| Radiochemical purity | >90% |
| Endotoxins | <17.5 EU per mL |
| Acetone | <5000 ppm |
| Ethanol | <10% |
| Radionuclidic | Half life +/- 30 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 the 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, $^{68}$Ga-DOTATOC and free Ga-68 can be differentiated at $R_f$ – 0.0 and 1.0, respectively.

**Sterility:** Following release, Tryptic Soy Broth (TSB) and Fluid Thioglycollate Media (FTM) are inoculated, incubated (TSB at 22.5 °C, FTM at 32.5 °C) and checked for growth during the ensuing 14 days.

**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 . Additional standard operating procedures include out of specification investigations and reprocessing in the event of a 0.22 micron filter failure.

CMC REFERENCES:

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**V. Labeling**

The final product vial containing $^{68}$Ga-DOTATOC will be appropriately labeled. The label will include: the name of the radiopharmaceutical, total activity, total volume, radioactive concentration (in mCi/mL), specific activity (in MBq/nmol and mCi/μmol), reference date/time and expiration date/time. The label will also clearly state that this is a new drug and is limited by Federal (or United States) law to investigational use.

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 root cause analysis for a failure-to-perform of a given investigational PET/CT scan.

**VI. 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 measuredradiation 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[2]. 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.

**VII. Previous Human Experience**

**Experience at the University of Iowa**

Although there is extensive use of $^{68}$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" in March 2011. Subjects received two $^{68}$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. $^{68}$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 $^{68}$Ga-DOTATOC PET compared to Octreoscan™; biodistribution and reproducibility for these five subjects is summarized in **Fig 4** &**Table 4**.

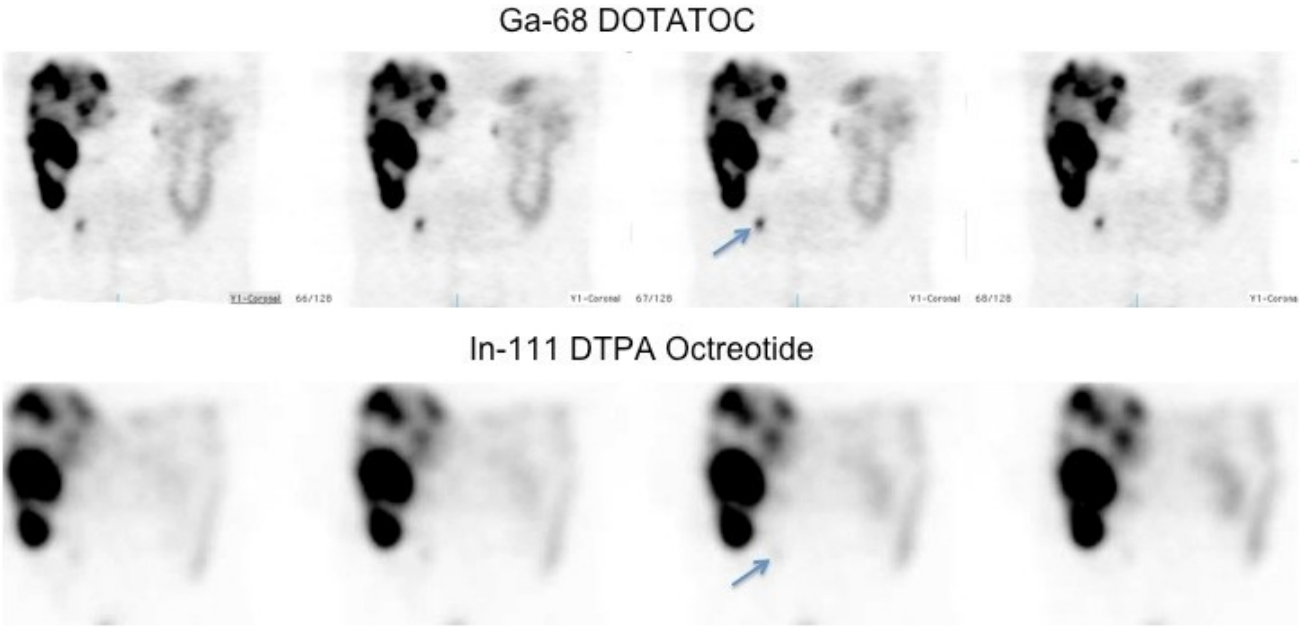


**Figure 3.** $^{68}$Ga-DOTATOC PET/CT in a patient with biomarkers and liver mets suggestive of ileal NET, but primary not visualized on either high-resolution, contrast CT or Octreoscan. Arrows indicate ileal lesion clearly demonstrated on $^{68}$Ga-DOTATOC PET/CT that was (in retrospect) faintly visible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

**Table 4. $SUV_{max}$ reproducibility of [$^{68}$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** | 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 $^{68}$Ga DOTATOC, 5 patients with metastatic NET underwent two DOTATOC PET scans. Standardized uptake values (SUVmax) 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 involved organ. Percentage error (i.e. reproducibility) was calculated for each lesion as ***Percentage Error = 100*ABS (Scan 2-Scan 1)/((Scan 2 + Scan 1)/2))***[13].

*mean ± standard deviation

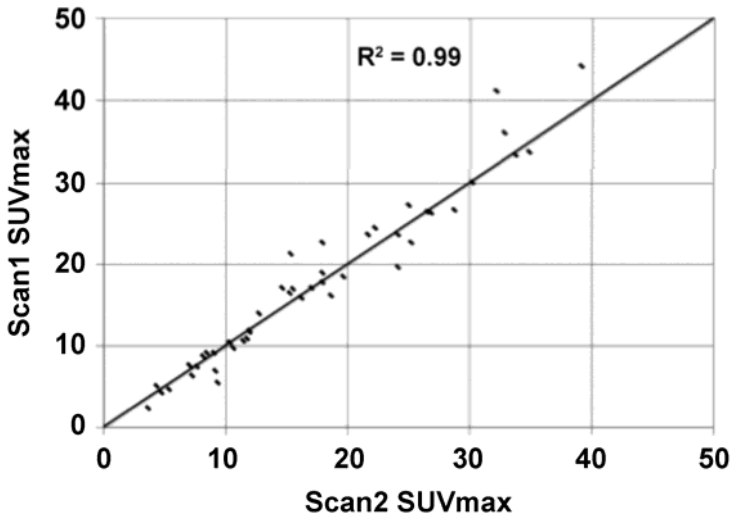


**Figure 4.** Reproducibility of $^{68}$Ga-DOTATOC PET in patients with NET. Results for each subject and all target lesions in Table 4 are shown. The average (mean ± SD) reproducibility was 10% ±10% for 50 target lesions. The scatter graph (excluding 2 lesions with SUV>50 for display purposes) shows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

The data analysis of our current safety and efficacy study is ongoing. There were no Grade 2 or higher Grade adverse events that were possibly related to Ga-68 DOTATOC in 195 administrations of the radiopharmaceutical. A preliminary analysis of the data of 70 patients, 46 of them matching the inclusion criteria of the current study, revealed a change in management in 39% of patients.

### Production of $^{68}$Ga- DOTATOC at University of Iowa

The cGMP grade DOTATOC was purchased from Bachemwith the written permission of Molecular Insight Pharmaceuticals, Inc. Radiolabeling was performed using a $TiO_2$ 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, radionuclic, sterility as shown in Table 4.

### European Experience in Humans

The potential of $^{68}$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

**Table 4. Performance of [$^{68}$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$^{-1}$) | Dose Calibrator | 20 MBq nmole$^{-1}$ | 31±4 | 100 |
| Acetone (ppm) | Gas Chromatography | < 5000 ppm$^{\alpha}$ | 399±64 | 100 |
| Ethanol (%) | Gas Chromatography | < 10% | 5±0 | 100 |
| Endotoxins EU mL$^{-1}$ | Limulus Amebocyte Lysate | < 175 EU$^{\S}$ mL$^{-1}$ | 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 $N_2$ Stream | 2 bar | Pass | 100 |

image quality in comparison to [$^{111}$In]DTPA-octreotide SPECT[14]. Although we have successfully employed [$^{111}$In]DTPA-octreotide SPECT/CT (Octreoscan™) + a diagnostic CT for diagnosis, staging, and monitoring of NET in children and adults[15,16], our RDRC approved studies (**Figures 3 and 4**) as well as comparisons of 68Ga-DOTATOC and Octreoscan™ by European investigators, support our hypothesis that 68Ga-DOTATOC will provide at least equivalent, and likely objective improvements in, diagnosis and staging of neuroendocrine tumors and other somatostatin receptor positive tumors[17-19]. Several advantages of 68Ga-DOTATOC PET/CT have been pointed out through these published studies. For example, Gabriel and colleagues concluded that 68Ga-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 68Ga-DOTATOC PET was superior to Octreoscan™ in detection of metastases in the lung, skeleton, liver, and brain[10]. A study demonstrating that $^{68}$Ga-DOTATOC PET influences patient management in ≥ 33% of patients further supports the introduction of this imaging technique into the United States[20].

Comparisons of $^{68}$Ga-DOTATOC and Octreoscan by European investigators support our early observations that $^{68}$Ga-DOTATOC will provide at least equivalent, and likely objective improvements in, diagnosis and staging of NETs[17-19]. Several advantages of $^{68}$Ga-DOTATOC PET/CT have been observed through these published studies. For example, Gabriel and colleagues concluded that $^{68}$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 $^{68}$Ga-DOTATOC PET was superior to Octreoscan in detection of NET metastases in the lung, skeleton, liver, and brain[10]. A study demonstrating that $^{68}$Ga-DOTATOC PET influences patient management in ≥ 33% of patients further supports our proposed research[20].

**VIII. Request for Permission to Charge for an Investigational Drug under an IND**

This application is seeking FDA approval to charge for the cost of producing $^{68}$Ga-DOTATOC to be used as a PET tracer. Costs are justified under Title 21, Chapter 1, Subchapter D Drugs for Human Use, Part 312, IND application as outlined below:

312.8b (i). $^{68}$Ga-DOTATOC PET will be used in this clinical trial as a replacement for Octreoscan™ SPECT imaging. As stated in our IND application, the primary advantage of Ga-68 based somatostatin receptor PET imaging over OctreoScan SPECT is the higher imaging resolution and accurate quantitation of uptake due to robust attenuation correction. The improved resolution and quantitation of uptake obtained with $^{68}$Ga-DOTATOC PET 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 $^{68}$Ga-DOTATOC with Octreoscan found $^{68}$Ga-DOTATOC to be superior in detection of skeletal and pulmonary involvement of neuroendocrine tumors_ENREF_10[10]. Additional advantages for patients include the lower radiation dose and the shorter imaging time. 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, $^{68}$Ga-DOTATOC (68 min half life) uses 185 MBq with an effective dose equivalent of 0.46 rads. In addition, $^{68}$Ga-DOTATOC PET/CT can be completed within 2 hours compared to an Octreoscan™ which requires 3 visits over 24 hours, making $^{68}$Ga-DOTATOC a much more convenient imaging choice for patients.

312.8b (ii). The imaging trial proposed under this IND will enroll up to 200 subjects, ages 6 months – 100 years of age with Somatostatin receptor positive tumors, many of whom will have had a recent Octreoscan™ and/or high-resolution, contrast-enhanced CT or MRI. The tumor types include neuroendocrine tumors, neuroblastoma, medulloblastoma, and pheochromocytoma. The study will thus test both efficacy and safety in adults and children with multiple tumor types.

312.8b(iii). $^{68}$Ga-DOTATOC will be produced at the University of Iowa PET Center. The extraordinary cost of producing $^{68}$Ga-DOTATOC precludes performance of the study without charging due to manufacturing complexity. The direct costs include purchase and storage of the synthetic peptide,

DOTATOC; a gallium generator every 6 months to produce the short lived isotope; chemicals required in the radiolabeling procedure; a specialized ModularLab™ to ensure reproducibility of the product and safety of the radiochemists; single use radiolabeling cassettes to ensure sterility of the product; personnel costs for the radiochemists; and the base cost of the PET/CT imaging.

312.8c. As $^{68}$Ga-DOTATOC has a 68 minute half-life, it will need to be produced locally when trials are expanded to other centers. We intend to provide the protocol as well as all required Standards of Procedure associated with this IND to the Society of Nuclear Medicine Clinical Trials Network. We will apply for expanded access charging at that time, if appropriate.

Charges will be paid by the subject or the subject's insurance company with the exception that the scans for children $\leq$ 17 yrs who may be paid from a childhood brain tumor research account in the University of Iowa Foundation.

## IX. References:


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## Appendix I

**HCCC Clinical Trial Data and Safety Monitoring Plan (DSMP)***
**Date:** 4/14/15
**IRB#:** 201503708
**Title:** Impact of Ga-68 DOTATOC PET-CT Imaging in Management of Neuroendocrine Tumors
**PI:** M Sue O'Dorisio, MD, PhD **Co-**PI: Yusuf Menda, MD

*** All investigator-initiated protocols will be subject to ongoing monitoring of accrual, subject eligibility, protocol modifications and continuing reviews. Active studies will be audited for the DSMC by the Clinical Research Safety Officer (CRSO), following guidelines based on level of risk to subjects. Audits will be conducted by reviewing subject files provided by clinical research coordinators, as well as original source documentation provided by online medical records and research pharmacists. The CRSO will review adverse events, eligibility of subjects, and adherence to the IRB- and PRMC-approved protocol. Protocols found to have discrepancies will be require a response from the PI and an action plan for correcting identified deficiencies. The DSMC will provide a schedule of audit and report dates if requested.*

**Type of Clinical Trial:**

- ☑ Investigator-initiated (UI/HCCC)
- ❑ Investigator-initiated, participating site
- ❑ Pilot study
- ❑ Phase I
- ❑ Phase I/II
- ☑ Phase II
- ❑ Phase III
- ❑ Compassionate-use drug protocol
- ❑ Interventional Treatment
- ☑ Interventional Non-Treatment
- ❑ Non-Interventional

**Study risk-level:**

- ❑ Level 1—low risk of morbidity or death, * <<1% of death or any adverse event

- ❑ 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% IND number: **114,398**
- ❑ Drugs being used on a "compassionate" basis

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

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**Subject inclusion/exclusion Criteria:**
Refer to Section III, page 6 of the protocol

**Subject Risks:**
Refer to Section III, pages 8-9 of the protocol

**Study Withdrawal/Discontinuation/Stopping Rules:**
Refer to Section III, pages 11-12 of the protocol

**Frequently used acronyms:**

| | |
|---|---|
| **CRF** | Case Report Form |
| **CRSO** | Clinical Research Safety Officer |
| **CTRM** | Clinical Trials Research Manager |
| **DSMC** | Data and Safety Monitoring Committee |
| **FDA** | Food and Drug Administration |
| **HCCC** | Holden Comprehensive Cancer Center |
| **ICF** | Informed Consent Form |
| **IND** | Investigational New Drug |
| **IRB** | Institutional Review Board |
| **PRMC** | Protocol Review and Monitoring Committee |

**Monitoring strategy based on risk-level:**

**Risk Level 4**

Interventional treatment trials involving investigational agents or devices with a risk of death* >5% or grade 4 – 5 SAE >15% (all investigator initiated INDs, and most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

An independent Study Monitor or the DSMC Chair (or designee), will review study data (provided by the PI and CRSO and communicate with the PI at least quarterly. A copy of this communication will be forwarded to the DSMC and PRMC Chairs. This communication may coincide with the Clinical Research Safety Officer's (CRSO) quarterly audit when possible. If an audit has not been conducted—due to lack of research activity--the quarterly summary letter will occur as scheduled.

- Subject accrual data will be obtained from OnCore on an ongoing basis by the Clinical Trials Research Manager (CTRM) during accrual review for the PRMC.
- The PI will provide an annual progress report to the DSMC and PRMC.
- The research coordinator or data manager for the study will register new subjects in OnCore. A scanned copy of the completed eligibility checklist will be attached in OnCore and available for review by the CRSO at the time of quarterly audits. OnCore will send an automatic notification to the CRSO when a subject's status is updated to eligible.
- Adverse events will be logged in OnCore for review by the CRSO during quarterly audits. Table I below provides reporting guidelines for routine adverse event reporting.
- Serious Adverse Events (SAEs) will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair, CRSO, and CTRM. Table II provides reporting guidelines.
- The CRSO will contact the research team quarterly to coordinate an audit of the trial's research records. Prior to the first audit of a trial the CRSO will schedule a meeting with the PI and/or study coordinator, and members of HCCC's Clinical Research Services. The purpose of this meeting will be to explain the auditing process to the PI/study team and to agree upon key elements of the trial that are critical to data integrity, outcome measures, and subject safety. OnCore auditing functionality will be used to conduct, evaluate, and report on each audit. Audits will:
    - verify eligibility of patients accrued to the study,
    - check for the presence of a signed informed consent,
    - determine compliance with protocol's study plan,
    - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
    - compare accuracy of data in the research record with the primary source documents,
    - review investigational drug processing and documentation,
    - assess cumulative AE/SAE reports for trends and compare to study stopping rules.

**Routine Adverse Event Reporting**

Adverse events attributed to the study drug will be reported to the HCCC DSMC *via* the CRSO following established standard operating procedure of the DSMC.

**Table I:** Routine Reporting of Adverse Events to the CRSO for IND 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 |

***Adverse Event Reporting Guidelines*** - This study will use the guidelines developed by the Cancer Therapy Evaluation Program (CTEP) for PET and/or SPECT IND agent

**Expedited Adverse Event Reporting**

Investigators MUST immediately report to the DSMC (via an SAE report in OnCore) any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). Reporting requirements are in Table II.

An adverse event is considered serious if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
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).

**Table II:** *Phase 1 and Early Phase 2 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.*

All serious adverse events must be reported to the DSMC within the timeframes detailed below.

| Hospitalization | Grade 1 and Grade 2 | Grade 3-5 |
|---|---|---|
| Resulting in inpatient hospitalization | 10 calendar days | 1 business day initial; 5 calendar day report |
| Not resulting in inpatient hospitalization | Not required | |

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

- "1 business day; 5 calendar days" - The AE must initially be submitted electronically using OnCore within 1 business day of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial notice.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

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 SAEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

Effective Date: May 5, 2011

**Reporting to the FDA**

It is the responsibility of the IND sponsor-investigator to comply with IND safety reporting as set forth in the Code of Federal Regulations, Section 312.32. This responsibility includes providing an annual IND report to the FDA. In addition:

- The FDA will be notified via phone (800-332-1088) or fax (800-FDA-0178) within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.
- The FDA will be notified via fax (800-FDA-0178) or online submission (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf) with a MedWatch (3500A or 3500) within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but not fatal or life-threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DSMC).

# Appendix II

## Sample Data Collection Forms for $^{68}$Ga-DOTATOC PET/CT

**Patient ID**_____

University of Iowa Hospital

**Inclusion / Exclusion Ga-68 DOTATOC PET Protocol**(IMPACT TRIAL)

**INCLUSION**

1. Y / N Age ≥ 6 months

2. Y / N Histologically diagnosed or suspected (pediatric only) neuroendocrine tumor or other tumor with probable somatostatin receptors subtype 2

3. Y / N Karnofsky performance status or Lansky Play Scale status of ≥ 60 (or ECOG/WHO equivalent)

4. Y / N Subject is male; or is a female who is either, surgically sterile (has had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (> 1 years without menses), ≥60 years old, or of childbearing potential for whom a pregnancy test (with the results known prior to investigational product administration) is negative. A negative 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 not capable of becoming pregnant. Female must also be non-lactating.

**EXCLUSION**

1. Y / N Subject weighs more than 400 pounds. (Subjects who weigh more than 400 pounds will not be able to fit inside the imaging machines.)

2. Y / N Inability to lie still for the entire imaging time (due to cough, severe arthritis, etc.)

3. Y / N Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc.)

4. Y / N Does the subject have any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the investigator, may significantly interfere with study compliance?

5. Y / N Peptide receptor radionuclide therapy (PRRT) within 4 weeks of Ga-68 DOTATOC PET/CT scan

6. Y / N Treatment with Sandostatin LAR within 4 weeks, SQ Octreotide within 12 hours, or Lanreotide injection within 8 weeks of Ga-68 DOTATOC PET/CT (+/- 5%)

_____ _____

Signature of screening MD Date

**Patient ID**_____

# Data Collection for Imaging Visit

## Subject Data (IMPACT TRIAL)

1) Limited Physical Exam:

**Weight _____ Height _____ BP ___/____ RR _____ P_____ Temp _____**

a) HEENT (Circle or fill in blank): NORMAL **OR**_____

b) Chest (Circle or fill in blank): NORMAL **OR**_____

c) Cardiovascular(Circle or fill in blank): NORMAL **OR**_____

d) Abdomen (Circle or fill in blank): NORMAL **OR**_____

e) Integument (Circle or fill in blank): NORMAL **OR**_____

f) Musculoskeletal (Circle or fill in blank): NORMAL **OR**_____

g) Neurological (Circle or fill in blank): NORMAL **OR**_____

---

Investigator (Signature)_____(Date) _____

**Patient ID:_____**

**Data Collection for $^{68}$Ga-DOTATOC PET/CT** (IMPACT TRIAL)

**This page will be completed in the PET Center: Date_____**

1) Pregnancy test (urine) required? Y / N Results_____

2) Ga-68 DOTATOC Dose:_____mCi @ Injection Time_____:_____

3) Uptake period _____min.

4) Vital Signs (supine) at PET Completion: P _____, BP _____/_____, RR_____ Temp _____ °C

5) Were any adverse events reported or observed since the $^{68}$Ga-DOTATOC injection?

☐ No ☐ Yes

If yes, provide a narrative of what the patient reported and/or what was observed.

_____

_____

_____

_____

_____

_____

Signature of PET staff: _____ Date / Time: _____

**Karnofsky/Lansky Performance Status**

This Karnofsky/Lansky performance status is used to determine the functional status of a subject. Performance status is a critical data field that has been determined to be essential for all outcome-based analyses. The Karnofsky Scale is designed for recipients aged 16 years and older, and the Lansky Scale is designed for recipients less than 16 years old. Use this scale to determine the score (10-100) that best represents the subject's activity status at the requested time point.

| **Karnofsky Scale (subject age > 16 years)** | | **Lansky Scale (subject age <16 years)** | |
|---|---|---|---|
| **Able to carry on normal activity; no special care is needed** | | **Able to carry on normal activity; no special care is needed** | |
| **100** | Normal, no complaints, no evidence of disease | **100** | Fully active |
| **90** | Able to carry on normal activity | **90** | Minor restriction in physically strenuous play |
| **80** | Normal activity with effort | **80** | Restricted in strenuous play, tires more easily, otherwise active |
| **Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed** | | **Mild to moderate restriction** | |
| **70** | Cares for self, unable to carry on normal activity or to do active work | **70** | Both greater restrictions of, and less time spent in active play |
| **60** | Requires occasional assistance but is able to care for most needs | **60** | Ambulatory up to 50% of time, limited active play with assistance/supervision |
| **50** | Requires considerable assistance and frequent medical care | **50** | Considerable assistance required for any active play, fully able to engage in quiet play |
| **Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly** | | **Moderate to severe restriction** | |
| **40** | Disabled, requires special care and assistance | **40** | Able to initiate quite activities |
| **30** | Severely disabled, hospitalization indicated, although death not imminent | **30** | Needs considerable assistance for quiet activity |
| **20** | Very sick, hospitalization necessary | **20** | Limited to very passive activity initiated by others (e.g., TV) |
| **10** | Moribund, fatal process progressing rapidly | **10** | Completely disabled, not even passive play |

Signature:_____Date:_____Time:_____

***DOTATOC PET-CT Case Evaluation Pre-Scan*** ***Patient ID:_____***

***I. Indication of Ga-68 DOTATOC PET-CT*** *(check one)*

☐Initial staging of pathologically proven NET
☐Restaging after completion of treatment to detect residual disease
☐Suspected recurrence of previously treated NET
☐Monitoring response during therapy of NET

***II. YOUR WORKING STAGE FOR THE PATIENT BEFORE Ga-68 DOTATOC PET-CT IS:*** *(check one)*

☐No evidence of disease / In remission
☐Primary disease only / Local recurrence
☐Liver metastases only
☐Metastases in multiple sites
☐Metastases with unknown primary
☐Unknown or uncertain

***III. PRIOR TREATMENT***

Other previous therapy? *(check ALL that apply)*

☐Surgery for primary tumor or metastasis
☐Chemotherapy
☐External beam radiotherapy
☐Hepatic directed therapy (SIR-spheres, bland embolization, chemoembolization
☐PRRT (type_____)
☐Octreotide / Lanreotide
☐None

***IV. CURRENT TREATMENT***

☐ Octreotide LAR or Lanreotide
☐ m-TOR inhibitors (i.e. everolimus) or TK inhibitors (i.e. sunitinib)?
☐ Other chemotherapy_____
☐ Other treatment_____
☐ None

If on treatment, what is your current impression (before PET) of your patient's response to currently ongoing therapy? (check one)

☐Clearly responding, but uncertain about degree of response
☐Possible partial response, but uncertain about degree of response
☐Suspect no response
☐Suspect progressive disease

***V. MANAGEMENT / THERAPY***

If $^{68}$Ga-DOTATOC PET were not available, your current management strategy would be? (check all that apply)

☐Observation (with close follow-up)
☐Additional Imaging (CT, MRI) or other non-invasive diagnostic tests
☐Tissue Biopsy (surgical, percutaneous, or endoscopic)
☐Octreotide LAR
☐Surgery for primary tumor / debulking surgery
☐Liver directed therapy/Liver transplant
☐PRRT
☐Chemotherapy or Other Biologic Modifiers (m-TOR inhibitors and/or TK inhibitors)
☐ Palliative External Beam Radiation Therapy
☐ Other Supportive care

Signature:_____Date:_____Time:_____

***DOTATOC PET-CT Case Evaluation Post-Scan*** ***Patient ID*** _____

**I. Compared to your Pre-PET assessment, your impression of overall extent of disease is?**
(choose only one)
☐More extensive
☐No change
☐Less extensive

**II. Did the PET scan show evidence of cancer activity that was not previously documented?**

☐Yes
☐No

**III. Your Post-PET working clinical staging is: (select only one)**

☐No evidence of disease / In remission
☐Primary Disease only / Local Recurrence
☐Liver metastases only
☐Metastases in multiple sites
☐Metastatic (distant) with unknown primary
☐Unknown or uncertain

**IV. In light of the PET findings, which of the following management/treatment strategies are you now planning or have you already undertaken? (check all that apply)**

☐Observation (with close follow-up)
☐Additional Imaging (CT, MRI) or other non-invasive diagnostic tests
☐Tissue Biopsy (surgical, percutaneous, or endoscopic)
☐Octreotide LAR
☐Surgery for primary tumor / debulking surgery
☐Liver directed therapy/Liver transplant
☐PRRT
☐Chemotherapy or Other Biologic Modifiers (m-TOR inhibitors and/or TK inhibitors)
☐ Palliative External Beam Radiation Therapy
☐ Other Supportive care

Signature:_____ Date:_____ Time:_____

**V. Was there a change in management in light of the PET findings?**

☐No Change
☐Minor Change
☐Major Change

Signature:_____ Date:_____ Time:_____

**Patient ID:**_____

# Ga-68 DOTATOC PET Adverse Event Questionnaire

**Please only list AEs that are new and have happened since the Ga-PET scan.**

| POSSIBLE ADVERSE EVENTS | YES/NO | COMMENTS/NOTES |
|---|---|---|
| **BODY AS A WHOLE** | | |
| Pain (abdominal) | | |
| Pain (chest/breast) | | |
| Pain (other/site) | | |
| Fever | | |
| Injection site reaction | | |
| | | |
| **CARDIOVASCULAR SYSTEM** | | |
| Flushing (vasodilatation) | | |
| | | |
| **DIGESTIVE SYSTEM** | | |
| Nausea | | |
| Diarrhea | | |
| Vomiting | | |
| | | |
| **RESPIRATORY SYSTEM** | | |
| Dyspnea (shortness of breath) | | |
| | | |
| **SKIN & APPENDAGES** | | |
| Rash | | |
| Itching (pruritus) | | |
| Hives (urticaria) | | |
| Sweating | | |
| Cyanosis (finger or toe discoloration) | | |
| | | |
| **CENTRAL NERVOUS** | | |
| Visual disturbances | | |
| Numbness of feet | | |
| Numbness of fingers/hands | | |
| Weakness of feet | | |
| Weakness of fingers | | |
| Burning sensation in feet | | |
| Burning sensation in fingers | | |
| | | |

Signature:_____ Date:_____ Time:_____