**Official Title: [$^{68}$Ga]DOTATATE-PET/MRI in Hepatocellular Carcinoma to Assess the Feasibility of Targeted Radionuclide Therapy with Somatostatin Receptor Ligands**

**NCT Number: NCT03648073**

**Document Date: September 27, 2018**

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**University of Alabama at Birmingham**
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**Protocol UAB 18-107:** **[$^{68}$Ga]DOTATATE-PET/MRI in Hepatocellular Carcinoma to Assess the Feasibility of Targeted Radionuclide Therapy with Somatostatin Receptor Ligands**

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**Study Supported By**

**UAB**
**Study Sponsor**

**Ga-68 DOTATATE**
**Study Agent**

**Pending**
**IND Number**


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# 1.0 Introduction and Study Rationale

## 1.1 Overview

There is great need for new therapeutic options for patients with hepatocellular carcinoma (HCC). This study will assess the feasibility of a novel theranostic approach to hepatocellular carcinoma (HCC) using [$^{68}$Ga]DOTATATE, a recently FDA-approved positron emission tomography (PET) ligand for imaging somatostatin receptor (SSTR) positive tumors. This PET tracer is in routine clinical use for neuroendocrine tumors (NET) but to our knowledge has not been systematically applied to HCC. The objective of this study is to measure the frequency of SSTR positivity in hepatocellular carcinoma using [$^{68}$Ga]DOTATATE-PET. We hypothesize that [$^{68}$Ga]DOTATATE-PET will be positive in at least 20% of patients with HCC. If this current study shows a substantial fraction HCCs have moderate to high SSTR levels based on PET imaging, this result would justify future studies evaluating targeted radionuclide therapy (TRT) with the therapeutic SSTR ligand [$^{177}$Lu]DOTATATE which was recently FDA approved for treating SSTR-positive NETs arising from the gastrointestinal tract.

**Study objective:** Determine the frequency of somatostatin receptor positivity in hepatocellular carcinoma using [$^{68}$Ga]DOTATATE-PET

*Hypothesis: [$^{68}$Ga]DOTATATE PET will be positive in at least 20% of patients with hepatocellular carcinoma (HCC).*

In this study, patients with treatment-naïve HCC (n=15) and patients with previously treated HCC being referred for systemic chemotherapy and/or best supportive care (n=15) will be enrolled. Patients will undergo a single whole body [$^{68}$Ga]DOTATATE-PET/MRI to assess SSTR positivity of their HCCs. The percentage of patients with HCCs showing activity in their HCC greater than liver and/or spleen will be calculated.

## 1.2 Background and Rationale

HCC is the most common type of liver cancer and frequently arises in the background of hepatic cirrhosis. HCC and other liver cancers accounted for an estimated 40,710 cases and 28,920 deaths in the United States in 2017.[1] The five-year survival for patients with liver cancer confined to the liver is estimated at 31.1%, but prognosis for tumors that spread outside of the liver is much worse with 10.7% five-year survival for patients with regional lymph node metastases and 2.8% for patients with distant metastases.[1] The definitive treatment for HCC is liver transplantation, but frequently patients do not choose to undergo transplantation or are deemed ineligible. In recent years, locoregional therapies for HCC have become increasingly utilized, including transarterial chemoembolization, percutaneous ablation, external beam radiation, and radioembolization with $^{90}$Y-labeled microspheres. These treatments are frequently utilized as a bridge to transplantation, but can also be used for definitive therapy for HCC. However, once the tumor has been found to spread beyond the liver and adjacent lymph nodes, few systemic treatment options remain available to patients. The first systemic treatment option for HCC was sorafenib, a tyrosine kinase inhibitor which was approved in 2007 for treatment of advanced HCC

following a trial that demonstrated a 44% improvement in median overall survival when compared to placebo.[2] However, sorafenib is frequently not well tolerated by patients with side effects experienced by approximately 64.9% of patients, with diarrhea, hand-foot-skin reaction, nausea, and fatigue being the most common.[3] As a result, in 2017 a second-line tyrosine kinase inhibitor (regorafenib) was approved in patients with advanced HCC who have been unable to tolerate or progressed on sorafenib.

[$^{68}$Ga]DOTATATE (tradename NETSPOT) is a peptide-based radiopharmaceutical for positron emission tomography (PET) that was approved for clinical use in the United States in 2016 for the evaluation of somatostatin receptor (SSTR)-positive neuroendocrine tumors (NETs). This PET tracer binds to SSTRs on the surface of tumor cells with the highest affinity for the SSTR2 receptor which is overexpressed in neuroendocrine tumors. In patients with metastatic NETs, somatostatin analogues (e.g. octreotide and lantreotide) are a mainstay in control of symptoms, but do not treat the underlying metastatic disease. In 2018, the FDA approved a therapeutic analogue of DOTATATE ([$^{177}$Lu]DOTATATE, tradename Lutathera) for the treatment of SSTR-positive gastroenteropancreatic NETs. A key concept is that [$^{68}$Ga]DOTATATE-PET is used to evaluate metastatic NETs for SSTR expression and use this information to select potential candidates for [$^{177}$Lu]DOTATATE therapy. This theranostic approach can potentially be applied to other tumors that express adequate levels of SSTR.

SSTR expression has previously been demonstrated in the setting of HCC to varying degrees. A study of 53 resected HCCs demonstrated that membrane SSTR2 was reliably detected in HCC and could serve as a potential therapeutic target.[4] Multiple tissue-based studies demonstrate SSTR positivity in 20-50% of HCCs.[4-6] Additionally, SSTR2 expression in HCC was positively correlated with cytokeratin 19-9 expression, serum alpha-fetoprotein level, and poor differentiation, all of which are poor prognostic markers for patients with HCC.[4, 7, 8] Additional studies have confirmed SSTR expression in HCC with varying distributions of the SSTR receptor subtype expression.[5, 6] However, the fraction of HCCs have high enough levels of SSTR for [$^{177}$Lu]DOTATATE therapy has not yet been assessed. Therefore, it is our aim to use [$^{68}$Ga]DOTATATE-PET/MRI to assess tumor SSTR expression in patients with HCC before and after locoregional therapy. This research plan is a critical prerequisite for determining the feasibility of this theranostic approach to treating HCC. If we obtain positive results, these data will be critical for designing a combined imaging and therapeutic study in HCC using DOTATATE.

## 2.0 Study Objectives

### Specific Aim 1: Determine the frequency of somatostatin receptor positivity in hepatocellular carcinoma using [$^{68}$Ga]DOTATATE-PET

*Hypothesis 1: [$^{68}$Ga]DOTATATE PET will be positive in at least 20% of patients with hepatocellular carcinoma (HCC).*

Liver transplantation is the only curative therapy for HCC and is an option for a selected subset of HCC patients. For those who are not candidates for transplantation, locoregional therapies with limited efficacy are available such as percutaneous ablation,

arterial chemoembolization, and Y-90 microsphere radionuclide therapies. There are few options for patients who progress or are not candidates for these therapies. The first line systemic therapy is sorafenib, a tyrosine kinase inhibitor. Sorafenib is often not well tolerated due to its side effects and there is need for additional systemic treatments.

## 3.0 Investigational Plan

### 3.1 Study Design

The project will be a pilot prospective IRB-approved HIPAA-compliant study that will enroll 15 patients with untreated HCC and 15 patients with previously treated HCC. These patients will be identified at weekly multidisciplinary hepatobiliary conference in collaboration with liver transplant surgery, interventional radiology, diagnostic radiology, hematology/oncology, gastroenterology, and radiation oncology. Patients will undergo standard-of-care treatment based on recommendations of hepatobiliary tumor board. The preferred imaging modality will be PET/MRI, owing to its superior soft tissue characterization of the liver and abdominal soft tissues when compared to non-contrast CT performed for PET/CT. However, understanding that patients may have large volume ascites or claustrophobia, PET/CT may be utilized as an alternative in select patients at the discretion of the Principal Investigator. The study will be performed within 4 weeks of most recent conventional anatomic imaging with either CT or MRI to minimize the potential to alter clinical management on the basis of the CT or MRI portion of the research examination.

### 3.2 Study Population

- Patients with treatment naïve hepatocellular carcinoma and patients with previously treated hepatocellular carcinoma being referred for systemic chemotherapy and/or best supportive care

### 3.3 Inclusion Criteria

- Known diagnosis of hepatocellular carcinoma, either by imaging criteria or pathology on biopsy
- Standard of care liver MRI or CT demonstrating viable HCC based on arterial contrast enhancement measuring at least 1.5 cm in largest axial dimension

### 3.4 Exclusion Criteria

- History of neuroendocrine tumor or other SSTR-positive tumor
- Current treatment with octreotide or lantreotide
- Interval locoregional therapy or new systemic therapy between standard of care liver MRI or CT study showing viable HCC and [$^{68}$Ga]DOTATATE-PET

### 3.5 Withdrawal Criteria

- Given that enrollment in this study will involve a single imaging exam, no withdrawal criteria will be used

- Patient charts will be followed for 12 months following PET to evaluate for outcomes

### 3.6 Replacement of Patients

- Given that enrollment in this study will involve a single imaging exam, no replacement of patients will be used

### 3.7 Study Duration

- Study enrollment and imaging will take place over 12 months

### 3.8 Safety Monitoring

#### 3.8.1 Data and Safety Monitoring Plan

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document. PET/MRI and PET/CT scans will be loaded into a separate password-protected image storage system that will not appear on the PACS utilized in clinical practice.

#### 3.8.2 Ethical Considerations

Given that the study involves a single imaging session with either PET/MRI or PET/CT and the expected age of the enrolled adult patients, ethical concerns regarding additional radiation exposure are minimal. If an unexpected potentially medically important finding is detected through participation in this study, the referring provider will be notified of the results to consider pursuing additional imaging or other diagnostic procedure.

## 4.0 Study Procedures

### 4.1 Informed Consent Procedure

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

### 4.2 Patient Registration

Enrollment in the study will be available after the patient has been seen by their treating physician at UAB. The majority of these patients are expected to be seen in Liver Transplant clinic. However, all patients that meet enrollment criteria are eligible.

Registration in the study will be performed by a research coordinator from the UAB Department of Radiology. Participation in the study is voluntary and choosing not to participate will not affect patient care in any way.

## 4.3 Initiation of Study

The PET tracer [$^{68}$Ga]DOTATATE is FDA-approved for gastroenteropancreatic neuroendocrine tumors and routinely produced for standard-of-care clinical PET through the UAB Cyclotron Facility and Radiopharmacy. The preparation of [$^{68}$Ga]DOTATATE for this study will be identical to the procedure used for producing clinical dosages. Additionally, UAB currently is performing clinical [$^{68}$Ga]DOTATATE-PET scans, including PET/CT and PET/MRI. Therefore, the study can be initiated immediately following institutional and IRB approval.

## 4.4 Drug Information

[$^{68}$Ga]DOTATATE is a radiolabeled peptide-based analogue of octreotide that is FDA-approved PET imaging agent for use in patients with gastroenteropancreatic neuroendocrine tumors. The radiotracer targets somatostatin receptors with highest affinity for SSTR2, which has been shown to be overexpressesd in hepatocellular carcinoma. The dosage of radiotracer administered to the patient is an intravenous weight-based dose of 2 MBq/kg (0.054 mCi/kg) up to a dose of 200 MBq (5.4 mCi). This results in an effective dose of up to 4.2 mSv (420 mrem) to the patient, which is equal to 1.4 years of natural background radiation exposure (3 mSv/yr).

## 4.5 Patient Assessment

Identification and workup of patients prior to potential enrollment in the study will follow standard-of-care procedures per the treating physician (hepatobiliary surgery, radiation oncology, etc.). If a patient is determined to be eligible for the study, the research coordinator in this study will be asked to come to the clinic to discuss potential enrollment.

## 4.6 Imaging Information

### 4.6.1 [$^{68}$Ga]DOTATATE PET Preparation and Injection

The injected dose will be an intravenous weight-based dose of 2 MBq/kg (0.054 mCi/kg) up to a dose of 200 MBq (5.4 mCi). The patient will be instructed to undergo standard patient preparation prior to DOTATATE PET/CT or PET/MRI. PET imaging will begin approximately 60 minutes following injection.

### 4.6.2 [$^{68}$Ga]DOTATATE PET/MRI Protocol

**Whole body imaging**

**Positron Emission Tomography Acquisition:** The patient will be placed on the PET/MRI scanner in the supine position. Initial localizer images will be obtained. Subsequently, static whole body images will be acquired from pelvis to skull base utilizing approximately eight 14 cm detector beds for 3-5 minute acquisitions per bed position. Correction for randoms, scatter, attenuation and reconstructions will be performed per the manufacturer's recommendations.

**Whole Body and Liver MRI:** Sequences performed will include MR attenuation correction (MRAC), axial and coronal T2 single shot fast spin echo and whole body Dixon-derived sequences.

Following whole body PET imaging, a routine MRI of the liver will be performed at UAB in the PET/MRI scanner per institutional protocol with and without the use of gadoteridol (Prohance) intravenous contrast via a weight-based dose of 0.2 ml/kg. An additional static abdominal PET acquisition will be performed concurrently.

The study protocol has been submitted to, reviewed, and approved by the UAB Radiation Safety Committee (OH&S Project 18-154).

The entire study is expected to take 60-90 minutes to acquire, with the whole body portion taking approximately 30 minutes and dedicated liver portion taking approximately 30 minutes.

### 4.6.3 [$^{68}$Ga]DOTATATE PET/CT Protocol

If the patient is unable to complete the PET/MRI scan or the patient is felt to be a suboptimal candidate for PET/MRI (due to large volume ascites, surgical clip artifacts, etc.), the patient will undergo whole body PET/CT.

**Whole body imaging**

**Positron Emission Tomography Acquisition:** The patient will be placed on the PET/CT scanner in the supine position. Initial localizer images will be obtained. Subsequently, static whole body CT images will be acquired from pelvis to skull base utilizing approximately eight 14 cm detector beds for 3-5 minute acquisitions per bed position. Correction for randoms, scatter, attenuation and reconstructions will be performed per the manufacturer's recommendations.

**Whole Body CT:** Patient will undergo a noncontrast non-optimized CT for anatomic localization of PET findings per institutional protocol (kVp 140, mA 400). The estimated dose of the CT exam is approximately 6 mSv, equal to approximately two years of background radiation.

The study protocol has been submitted to, reviewed, and approved by the UAB Radiation Safety Committee.

### 4.6.4 PET/CT and PET/MRI Imaging Interpretation and Storage

Images from the PET/CT and PET/MRI will be anonymized and subsequently stored and reviewed using a commercially available software package (MIM Encore, Cleveland, OH). The PET and whole body MRI studies will not be available in the UAB PACS system. This is in an effort to blind the treating physicians from making clinical decisions on an experimental imaging technique. The liver MRI images will be sent to clinical PACS and the medical record as part

of standard-of-care imaging and can be used in the clinical-decision making process. No formal interpretation will be generated for the [$^{68}$Ga]DOTATATE-PET or whole body MRI portion of the study.

PET/CT and PET/MRI images will be interpreted by board certified physicians specialized in molecular imaging and abdominal imaging. Images will initially be interpreted as positive or negative for SSTR-positive HCC. HCC lesions will be considered SSTR positive for the purposes of this study if they have higher [$^{68}$Ga]DOTATATE activity than adjacent liver not involved by HCC. The amount of [$^{68}$Ga]DOTATATE binding for intrahepatic HCCs will be further characterized based on visual analysis as less than skeletal muscle (no binding), higher than skeletal muscle but less than or equal to adjacent liver (low binding), higher than adjacent liver but less than spleen (moderate binding) or equal to or greater than spleen (high binding). For patients with SSTR-positive HCC and positive [$^{68}$Ga]DOTATATE PET, intrahepatic and extrahepatic disease will be assessed on MRI/CT alone first, with confidence in interpretation rated on a 1-5 scale (1 = negative, 5 definite). Following this, fused PET/CT or PET/MRI images will be assessed and rated on the same 1-5 scale.

#### 4.6.5 Safety Monitoring

Vital signs will be assessed immediately before and after injection of [$^{68}$Ga]DOTATATE (HR and supine BP). Patients will be monitored for adverse events during injection and after completion of the imaging study Additionally, patient's vitals (HR and supine BP) will be checked at the completion of the imaging study prior to leaving the imaging center.

#### 4.6.6 Patient Follow-Up

Patients will be instructed to contact the UAB Department of Radiology Advanced Imaging Facility if there are any concerns about delayed side effects related to the study radiotracer. Patients will be seen in the clinic if there are any concerning study related adverse events requiring further evaluation.

## 5.0 Study Parameters

### 5.1 Primary Endpoint

- Percentage of patients with moderate to high binding of [$^{68}$Ga]DOTATATE on PET examination
- Concordance between [$^{68}$Ga]DOTATATE PET results and liver MRI results

### 5.2 Study Termination

The study will stop enrolling patients once the target number has been reached.

## 6.0 Statistical Considerations

### 6.1 Study Design

This is a prospective pilot trial to determine the potential use of [$^{68}$Ga]DOTATATE PET for patients with hepatocellular carcinoma to assess feasibility of targeted radionuclide therapy with somatostatin receptor ligands. The primary objective of this study is to

determine if a sufficient fraction (20% or greater) of HCC seen on conventional anatomic imaging demonstrates levels of somatostatin receptor expression to result in a positive DOTATATE PET scan. If a sufficient fraction of patients demonstrate positive DOTATATE PET scans, this study could serve as the basis for a subsequent therapeutic clinical trial with [$^{177}$Lu]DOTATATE.

### 6.2 Sample Size Justification

As this is a pilot feasibility study, no formal hypothesis will be testing, and thus no power analysis was performed. The primary objective is to determine the frequency of somatostatin receptor positivity in hepatocellular carcinoma using [$^{68}$Ga]DOTATATE-PET. In this study, patients with treatment-naïve HCC (n=15) and patients with previously treated HCC being referred for systemic chemotherapy and/or best supportive care (n=15) will be enrolled through the UAB Hepatobiliary Tumor Board in order to estimate the percentage of patients with moderate to high binding of [$^{68}$Ga]DOTATATE on PET examinations. Patients will undergo a single whole body [$^{68}$Ga]DOTATATE-PET/MRI or PET/CT to assess SSTR positivity of their HCCs. If a sufficient fraction (20% or greater) of HCC seen on conventional anatomic imaging demonstrate levels of somatostatin receptor expression to result in a positive DOTATATE PET scan, a subsequent therapeutic clinical trial with [$^{177}$Lu]DOTATATE will be carried out. With a total of 30 patients enrolled, the estimated
percentage of positive binding of [$^{68}$Ga]DOTATATE will have two-sided 95% confidence intervals (CI) from $7.7\% \leq p \leq 38.6\%$ using the Clopper-Pearson (exact) method assuming at least 20% positive binding occurs. Although the confidence interval will be wide for each subgroup, e.g. treatment-naïve HCC or previously treated HCC with n=15 (95% CI $4.3\% \leq p \leq 48.1\%$), it will provide early evidence if the [$^{68}$Ga]DOTATATE binding will be affected by prior treatment and/or stage of disaese.

### 6.3 Definition of Analyzed Study Population

All patients who underwent a [$^{68}$Ga]DOTATATE-PET/MRI or PET/CT scan will be included in the analysis.

### 6.4 Statistical Analysis Plan

This study will largely be exploratory and descriptive. For all clinical and histological evaluations as well as imaging parameters, we will generate summary tabulations of the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the frequency and percentage for categorical variables. Analyses will be primarily descriptive and graphical in nature. The count, and percentage of patients with HCCs showing activity in their HCC greater than liver and/or spleen will be estimated using Clopper-Pearson (exact) method along with two-sided 95% CI. The estimation will be provided for all 30 patients first, and then by treatment-naïve or not.

Concordance between [$^{68}$Ga]DOTATATE PET results and liver MRI results for patients with SSTR-positive HCC and positive [$^{68}$Ga]DOTATATE PET, intrahepatic and extrahepatic disease will be assessed on MRI/CT alone first, with confidence in interpretation rated on a 1-5 scale (1 = negative, 5 definite). Following this, fused PET/CT or PET/MRI images will be assessed and rated on the same 1-5 scale. Scale 3-4

is defined as positive. The agreement(concordance) between nominal (e.g. scale 1-5) or binary outcome (positive or negative) of [$^{68}$Ga]DOTATATE PET results and liver MRI results will be assessed using Cohen's kappa coefficients with one-side 95% confidence intervals. Based on values of Cohen's kappa, the agreement will be considered as poor (>0.2), fair (0.21-0.40), modrate (0.41-0.60), good (0.61-0.80), and very good (0.81-1.0) (**Dtsch Arztebl Int.** Concordance Analysis .**2011 Jul; 108(30): 515–521.** PMID: **21904584**). Bland-Altman diagrams will be used to evaluate agreement for other continuous imaging variables between these two methods. All statistical analysis will be carried on SAS v9.4.

## 6.5 Data and Safety Monitoring Plan

### 6.5.1 Pre-Study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.
Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

### 6.5.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UAB IRB. Prior to obtaining IRB approval, the protocol must be approved by the by the UAB Comprehensive Cancer Center Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

### 6.5.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

### 6.5.4 Changes in the Protocol

Once the protocol has been approved by the UAB IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

### 6.5.5 Adverse Event Reporting

As with many IV administered agents, [$^{68}$Ga]DOTATATE could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in human exposure to date. Reasonable precautions will be taken, consistent with normal radiologic and clinical facility practice. The patient will be monitored until the PET procedure is completed, and trained personnel and emergency equipment will be available per facility standards.

Qualifying Adverse Events (AEs), including Serious Adverse Events (SAEs), as defined herein, will be reported via the FDA Adverse Event Expedited Reporting System (AERS). For the [$^{68}$Ga]DOTATATE IND we will report adverse events based on the FDA final rule for IND safety reporting requirements under 21 CFR part 312 published on September 29, 2010 and implemented on March 28, 2011. This investigational study is not a BA or BE study so 21 CFR part 320 is not applicable. Adverse events will also be reported to the UAB IRB according to their requirements.

Reporting of Serious Adverse Events (SAEs) to Advanced Accelerator Applications (AAA): In addition to reporting of SAEs to the responsible IRB and Health Authority, the Principal Investigator or designee will document all SAEs that occur following receipt of [$^{68}$Ga]DOTATATE (whether or not related to study drug) to AAA. Such SAEs must be reported within 24 hours of Principal Investigator or designee becoming aware of the event. All SAE information must be reported to https://www.adacap.com/contact-us/pharmacovigilance/.

Additional and further requested information (follow-up or corrections to the original case) will be detailed and faxed/emailed to the same address and must include the following minimum information: The name and contact information of the reporter, the name of the study drug(s), a description of the reported SAE, with the subject identified by one or more of the following (subject initials, subject number age, sex), an investigator assessment of study drug causality, and any additional data which would aid the review and causality assessment of the case including but not limited to the date of onset, severity, the time from administration of study drug(s) to start of the event, the duration and outcome of the event, any possible etiology for the event, and the final diagnosis or syndrome, if known. If AAA receives any individually identifiable health information collected or produced in the study, AAA shall use and disclose only for the purpose of complying with applicable laws, provided that all such uses are disclosed in the IRB-approved informed consent form. AAA will use all reasonable efforts to protect the privacy and security of individually identifiable health information and will require its business partners to do so also. AAA will not contact any study subjects, unless permitted by the informed consent form.

#### 6.5.5.1 General Definitions (from 21 CFR 312.32 (a))

Adverse Event (AE): An Adverse Event is an untoward medical occurrence associated with the use of the drug in humans, whether or not considered

drug related. For this study, the drug is [$^{68}$Ga]DOTATATE and adverse events would include any events experienced by a study participant during the Adverse Event reporting period defined in Table 1 whether or not it was considered to be related to the [$^{68}$Ga]DOTATATE. At the conclusion of the imaging study, the imaging technologist will observe the patient and also inquire if they are back to their usual state of health. If a negative answer is received, then the physician will be called to investigate this report as a possible adverse reaction.

Adverse Reaction: An Adverse Reaction is any adverse event caused by a drug. In this study, the drug is [$^{68}$Ga]DOTATATE.

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

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Investigational Agent: An investigational agent is any agent held under an Investigational New Drug (IND) application. For purposes of this study, [$^{68}$Ga]DOTATATE is the investigational agent.

**6.5.5.2 AE Reporting Requirements**

The investigators on this protocol will report any suspected adverse events that occur after [$^{68}$Ga]DOTATATE administration and within the specified follow-up period to Dr. Galgano and they will work together to determine whether there was an adverse event or adverse reaction and the severity of the adverse event or reaction.

All AEs will be followed by the investigators until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology is achieved, or until subject is lost to follow up.

**6.5.5.3 CAEPR/ASAE for [$^{68}$Ga]DOTATATE**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. The Agent Specific Adverse Event List (ASAEL) would include the expected adverse events associated with the use of [$^{68}$Ga]DOTATATE. At this time, there are no reported AEs associated with the use of a [$^{68}$Ga]DOTATATE in clinical studies. We will continue to update our CAEPR and ASAE lists as this study progresses, including by reviewing the literature and our in-house data safety monitoring. If any are found, we will begin an ASAE list. Any information on reported AEs for [$^{68}$Ga]DOTATATE will be provided by the sponsor to all of the investigators on this protocol.

**6.5.5.4 Potential but Unexpected AE for [$^{68}$Ga]DOTATATE**

There have been no reported AEs associated with the use of a [$^{68}$Ga]DOTATATE in clinical studies.

Other general risks for PET/CT and PET/MRI imaging include:

- The injection site may become infected.
- The dose might be extravasated into tissues surrounding the vein catheter leading to localized pain/discomfort.

Radiation risks: [$^{68}$Ga]DOTATATE injection contributes to lifetime radiation accumulation. The smallest dosage for imaging and safe handling are used for these protocols. The organ and total body doses associated with [$^{68}$Ga]DOTATATE imaging are comparable to those associated with other widely used clinical nuclear medicine procedures. The dose of the DOTATATE PET is approximately equal to 1.4 years of exposure to natural

background radiation. The dose of the CT scan is approximately equal to 2 years of exposure to natural background radiation.

**6.5.5.5 Review of Safety Information**

As required by 21 CFR 312.32(b), the physician investigators will promptly review all information relevant to the safety of the drug. The physician investigators will also be providing much of this information to the local IRB as well for data safety and review monitoring. The review will include determining whether there is a safety event over time and the causality. Reporting will be as described in Table 1.

Characterization of the severity of an Adverse Event: Adverse events will be graded as below.

Grade: Grade denotes the severity of the AE. An AE is graded using the following categories:

- Mild
- Moderate
- Severe
- Life-threatening or disabling
- Fatal

NOTE: Severity is graded on the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) based scale for each adverse event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal hemoglobin values. "Severity" is NOT the same as "Seriousness." All appropriate clinical areas should have access to a copy of the most current CTCAE and a copy of the CTCAE can be downloaded from (http://ctep.cancer.gov).

Attribution of cause: The physician investigators will determine whether an adverse event was related to a medical treatment or procedure. Definitions taken from our work with CTEP and NIH give the following definitions for "Attribution" that we will adopt for this IND study: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure
- **NOTE:** Attribution is part of the assessment of an adverse event. Determining that an event is 'unlikely related' or 'unrelated' to a study agent or procedure does NOT make the event unreportable, or disqualify the event as an AE. As defined above, an AE is reportable as specified

herein if it occurred: **"during the Adverse Event reporting period defined in the protocol**, or by applicable guidance, regulation, or policy."

**6.5.5.6 Adverse Event Reporting**

Expedited AE reporting for this study will be done through the Cancer Consortium, IRB and FDA and as required by FDA MedWatch. These requirements are briefly outlined in the table below.

**Table 1. Reporting Requirements.**

| | **Unexpected** | | | **Expected** |
|---|---|---|---|---|
| | **Adverse Reaction (known or suspected attributable to the use of [$^{68}$Ga]DOTATATE** | | **AE not attributable to [$^{68}$Ga]DOTATATE** | **AE, AR** |
| | Serious including life-threatening (or death) | Nonserious | Life-Threatening or serious or not serious | None are expected for [$^{68}$Ga]DOTATATE |
| **Reporting Time Requirement to the FDA** | **Report to FDA ASAP and within 7 days of discovery of event** | Annual Continuation Review submission | Annual Continuation Review submission | Not applicable to [$^{68}$Ga]DOTATATE |
| **Reporting Form for the FDA** | IND Safety report of potentially serious risk | Annual Reports / Case reports | Annual Reports / Case reports | Not applicable to [$^{68}$Ga]DOTATATE |
| **Reporting Time Requirement to the local IRB** | **Report to IRB ASAP within 10 days of discovery of event** (suspected is defined as 50% probability attributable to [$^{68}$Ga]DOTATATE study) this also includes any increased risks with the study even without an AE | At continuation review time | At continuation review time | Not applicable to [$^{68}$Ga]DOTATATE |
| **Reporting form for the IRB** | Expedited Reporting Form for Unanticipated Problems or Noncompliance and Adverse Event Reporting Form | Form for Unanticipated Problems or Noncompliance, Case reports on continuation form, Data Safety | Form for Unanticipated Problems or Noncompliance, Case reports on continuation form, Data Safety Monitoring Reports | Not applicable to [$^{68}$Ga]DOTATATE |

| | | | | |
|---|---|---|---|---|
| | | Monitoring Reports | | |

#### 6.5.5.7 Expedited Adverse Reaction Reporting Guidelines

Life-threatening (or fatal) adverse reactions must be reported within 7 days to the FDA. The FDA should be notified as soon as the adverse reaction is discovered by telephone or fax or email. The instructions and forms are available at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm The report should be sent ASAP by mail and followed with a follow-up report. Individual IND safety reports to FDA are submitted on the Medwatch FDA Form 3500A as an "IND Safety Report". The form should be sent to The Director, Office of Generic Drugs in the Center for Drug Evaluation and Research at FDA. The address and phone numbers are available at: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm119100.htm.

All life threatening adverse reactions reports are submitted to the FDA, THE UAB IRB and to all investigators. A copy of the report is kept on file.

### 6.5.6 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

## 6.6 Data Management

All patient data will be anonymized and stored on encrypted password-protected computers with access only given to members of the research team. Standard precautions regarding HIPAA will be taken to avoid any breach in patient privacy.

## 7.0 References


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