^{68}Ga-DOTATATE PET/CT Assessment ofCardiac Sarcoidosis

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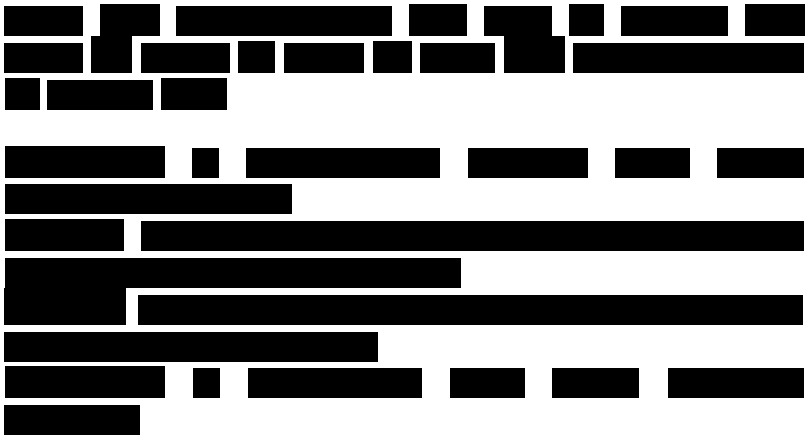


Funding Sponsor: CV Prospective Grant (FP00095637)

Study Product: ^{68}Ga-DOTATATE

Study Summary

Title	^{68}Ga-DOTATATE PET/CT Assessment of Cardiac Sarcoidosis
Study Design	Prospective study of 15 consecutive patients with suspected or newly diagnosed cardiac sarcoidosis (CS) who are referred for a clinically indicated ^{18}FDG (and $^{13}NH_3$) PET/CT scan for cardiac sarcoidosis (CS) will be approached to undergo a ^{68}Ga-DOTATATE PET/CT scan. Comparison will then be made between the ^{68}Ga-DOTATATE PET/CT and the ^{18}FDG and $^{13}NH_3$ PET/CT to determine if ^{68}Ga-DOTATATE detects CS.
Study Center(s)	Mayo Clinic, Rochester MN Campus
Primary Objective	To determine if ^{68}Ga-DOTATATE PET/CT will have a similar accuracy as ^{18}FDG and $^{13}NH_3$ PET/CT in diagnosing CS and if it will be able to do so without the need for complex patient dietary preparation that is required with ^{18}FDG PET/CT.
Number of Subjects	15 consecutive patients
Main Inclusion Criteria and Diagnosis	Primary inclusion criteria are 1) patients over the age of 18 years of age who are referred for clinically indicated ^{18}FDG and $^{13}NH_3$ PET/CT for cardiac sarcoidosis (CS) 2) have clinically suspected, or newly diagnosed CS 3) are not-pregnant or nursing 4) consent to undergo a ^{68}Ga-DOTATATE PET/CT scan. Diagnosis of CS by ^{68}Ga-DOTATATE will be determined by the presence or absence of myocardial uptake of ^{68}Ga-DOTATATE using similar methodology as previously reported (1,2).
Study Product, Dose, Route, Regimen, Duration	5.4 mCi of ^{68}Ga-DOTATATE will be administered by intravenous route. 60 minutes following administration, a low-dose transmission CT thorax scan will be performed for attenuation purposes followed by a cardiac PET emission scan obtained in the three-dimensional list mode.

Statistical Methodology	**Primary Efficacy Analysis:** Nominal continuous variables will be represented as the mean +/- SD and categorical variables will be noted as the number and percentage of total. Pearson chi-square test will be utilized to determine statistical significance for continuous variables whereas a Student's two-sample t-test will be implemented to determine statistical significance for continuous variables. Univariate and multivariate analyses will be performed when relevant. Statistical significance will be set a priori as a p-value less than 0.05. Concordance and discordance of ^{68}Ga-DOTATATE PET/CT with ^{18}FDG and $^{13}NH_3$ PET/CT for the presence or absence of CS will be calculated and utilizing ^{18}FDG and $^{13}NH_3$ PET/CT as the "gold-standard" for CS, the sensitivity and specificity of ^{68}Ga-DOTATATE for the detection of CS will be determined. All statistical analyses will be performed using JMP Pro 9 (SAS Institute INC. Cary, North Carolina). **Safety:** The overall safety profile will be assessed in terms of imaging agent related adverse events, and vital signs.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background/Rationale

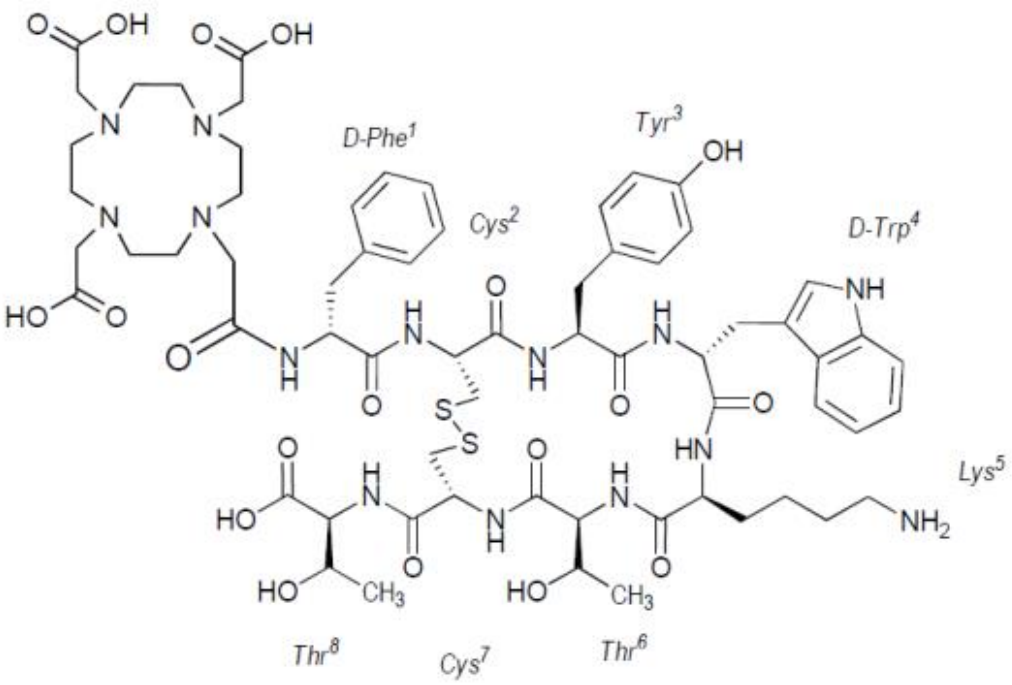
Optimizing our imaging capabilities for patients with CS is critical as it has diagnostic (3), prognostic (4) and therapeutic implications (5). However, our current diagnostic techniques have several limitations. Detection of CS by endomyocardial biopsy has sensitivity as low as 20% (6). Gallium-67 single photon emission tomography (SPECT) scintigraphy and echocardiography also have a reported sensitivity of 40% and 25% respectively (7,8). MRI has improved sensitivity for detection of CS at 75% (9) but may be problematic in CS patients with an intracardiac device. Perhaps more critical is that MRI lacks the ability to help differentiate active from inactive CS, which is critical for treatment planning and follow-up. Among the various invasive and noninvasive techniques, ^{18}FDG PET/CT has the highest sensitivity for the detection of CS (10) but requires specific dietary preparation that is difficult for patients to follow and is not completely effective at eliminating physiologic ^{18}FDG uptake. The latter may lead to inconclusive scan results in up to 30% of patients undergoing ^{18}FDG PET/CT imaging for CS (11-16). Furthermore, the dietary preparation is particularly challenging for diabetic patients. A more ideal PET/CT tracer for CS imaging that would not demonstrate physiologic myocardial uptake, and therefore would not require special dietary preparation, would streamline our diagnostic practice and thereby benefit our patients. Moreover, such an agent would eliminate the need for extra staffing time to discuss dietary procedures with patients and ultimately lead to fewer studies needing to be cancelled or repeated due to uncertain results. ^{68}Ga DOTATATE is a radiotracer targeted to somatostatin receptors which has been recently FDA and CMS approved to image neuroendocrine tumors (17). However, ^{68}Ga-DOTATATE may also be utilized off-label to image activated inflammatory cells, including macrophages and multinucleated giant cells that accumulate in granulomatous inflammation such as in sites of CS. When activated, these cells express somatostatin receptors in high abundance. Ga-DOTATATE binds to these receptors, and therefore labels sites of active CS which can be then detected on a PET/CT scanner (18). ^{68}Ga-DOTATATE, however, is not taken up in normal myocardial tissues (2). Therefore, unlike ^{18}FDG, CS imaging with ^{68}Ga-DOTATATE may obviate the need for complex patient preparation protocols and consequently may limit the incidence of uninterpretable scans, improve patient satisfaction and potentially improve diagnostic accuracy.

1.2 Radioisotope

1.2.1 **^{68}Ga-DOTATATE** (information 1.2.1.1-1.2.1.3 provided by the Food and Drug Administration (FDA) (https://www.accessdata.fda.gov/drugsatfda).

1.2.1.1 Description

"Dotatate, also known as **DOTA-0-Tyr3-Octreotate**, is a cyclic 8 amino acid peptide with a covalently bound chelator (dota). The peptide has the amino acid sequence: H-D-Phe-Cys-Tyr-D-Trp-Lys-ThrCys-Thr-OH, and contains one disulfide bond. Dotatate has a molecular weight of 1435.6 Daltons." Figure from FDA.gov.



1.2.1.2 Mechanism of Action

"Ga 68 dotatate binds to somatostatin receptors, with highest affinity for subtype 2 receptors (sstr2). It binds to cells that express somatostatin receptors including malignant cells, which overexpress sstr2 receptors. Gallium 68 (Ga) is a β+ emitting radionuclide with an emission yield that allows positron emission tomography (PET) imaging."

1.2.1.3 Pharmacokinetics

"Distribution Ga 68 dotatate distributes to all sstr2-expressing organs such as pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands. There is no uptake in the cerebral cortex or in the heart, and usually thymus and lung uptakes are low.

Elimination A total of 12% of the injected dose is excreted in urine in the first four hours post-injection."

1.2.1.4 Dose

5.4 mCi of ^{68}Ga-DOTATAE will be administered.

1.2.1.5 Cardiac Experience

There are three critical components to support feasibility of the proposed project: 1) Clinically indicated ^{18}FDG PET/CT (performed with $^{13}NH_3$ PET/CT as the standard of care) is already being performed at Mayo Clinic Rochester routinely with an average 4-5 studies per week and preliminary data have been presented at national meetings based upon these studies, (19) (20) 2) The use of ^{68}Ga-DOTATATE to image CS is predicated upon sound scientific reasoning, and 3) There are initial reports that ^{68}Ga-DOTATATE may in fact be able to image CS.

1) ^{18}FDG PET/CT can detect CS but is imperfect: PET/CT/ has proven to have the highest diagnostic accuracy for the detection of CS (10) with a reported sensitivity of 89% (10) and specificity as high as 97% (21). However, these results are predicated upon sufficient dietary preparation. Unfortunately, dietary preparation is often inadequate (11). Indeed, in our own MCR patient population, one-fifth of patients had suboptimal dietary preparation which ultimately compromised image quality and test accuracy (19). As a result, multiple efforts have been undertaken to enhance dietary preparation for ^{18}FDG PET/CT CS imaging (12-15). Despite these ongoing efforts, there remains no uniform means for dietary preparation. Furthermore, these preparation procedures are onerous and include strict fasting, specific diet adherence and potentially the use of heparin. This is likely the reason for poor compliance with dietary preparations (16). It also requires extra nuclear laboratory personnel time to contact patients and instruct them regarding the dietary procedures. For patients with diabetes mellitus, additional coordination must be made with the Department of Endocrinology. Given these issues, further efforts are warranted to identify another means by which to accurately image patients with known or suspected CS.

   FDG PET/CT for detecting CS also requires the concomitant use of myocardial perfusion PET/CT or SPECT imaging as the standard of care (cite SNMMI/ASNC expert consensus document), given the issues of physiologic FDG uptake and nonspecific findings and the potential for scar detection. This is associated with increased costs, greater cyclotron (if and $^{13}NH_3$ ammonia is used) and labs efforts, more patient time, and additional radiation exposure. A single scan with a single tracer has the potential to reduce effort and costs and increase patient satisfaction.

   ^{18}FDG PET/CT in CS Feasibility at Mayo Clinic: The multidisciplinary team we have assembled at Mayo Clinic has developed expertise in diagnosis and care of the CS population (12,13,19,20,22-26). Furthermore, we have one of the largest, if not largest CS practice in the nation with approximately 4-5 patients undergoing ^{18}FDG PET/CT per week. This has allowed our technicians and nursing staff along with our physicians to

create a streamlined practice in performing cardiac imaging in this patient population. As a result our physician team members are lead authors on national guidelines (24) and our technicians are conducting national talks to educate other imaging staff on optimizing ^{18}FDG PET/CT in CS (19).

2) The use of ^{68}Ga-DOTATATE is predicated upon sound scientific reasoning: ^{68}Ga-DOTATATE is a somatostatin receptor targeted radiotracer traditionally used to image neuroendocrine tumors (17). However, ^{68}Ga-DOTATATE may also be utilized to image inflammatory cells typically seen in CS, including macrophages and multinucleated giant cells, because these cells express somatostatin receptors (18). ^{68}Ga-DOTATATE, however, is not taken up in normal myocardial tissue (2). Therefore, unlike ^{18}FDG, CS imaging with ^{68}Ga-DOTATATE may obviate the need for complex patient preparation protocols and consequently may limit the number of uninterpretable scans, improve patient satisfaction and potentially improve diagnostic accuracy.

3) Initial reports of ^{68}Ga-DOTATATE for CS: There are two studies of which the investigators are aware that examine the feasibility of somatostatin receptor ligands, such as ^{68}Ga-DOTATATE, to image CS. The initial study compared PET/CT imaging with a radiolabeled somatostatin receptor ligand to cardiac magnetic resonance imaging (CMR) for detection of CS (1). This study demonstrated a 96.1% concordance rate between the two imaging modalities and concluded that the use of a somatostatin receptor ligand to detect CS was feasible. The second investigation imaged 19 patients with suspected CS with both ^{18}FDG PET/CT and ^{68}Ga-DOTATATE (2). The authors demonstrated that ^{68}Ga-DOTATATE outperformed ^{18}FDG PET/CT with a100% accuracy for the detection of CS and a 100% inter-observer agreement in regards to the ^{68}Ga-DOTATATE results. Both of these studies offer evidence that ^{68}Ga-DOTATATE will be a promising agent for the detection of CS.

^{68}Ga-DOTATATE Feasibility at Mayo Clinic: Mayo Clinic is a leader in ^{68}Ga-DOTATATE production and imaging having already imaged over 400 oncologic patients since October 2016. Furthermore, Mayo Clinic has proven expertise in the production of 68Ga-DOTATATE with patents currently pending. Finally, members of the current grant application team (GJ and AK) are nationally recognized in the developing field of ^{68}Ga-DOTATATE imaging (27).

2 Study Objectives

To determine if ^{68}Ga-DOTATATE PET/CT imaging will have a similar accuracy as ^{18}FDG PET/CT with $^{13}NH_3$ in diagnosing CS and if it will be able to do so without the need for complex patient dietary preparation that is required with ^{18}FDG PET/CT.

3 Study Design

The proposed investigation is a feasibility study designed to assess the efficacy of ^{68}Ga-DOTATATE PET/CT imaging in the CS population. We propose imaging 15 consecutive patients initially (with an intention to do a larger study) with the standard of care approach of both ^{18}FDG and $^{13}NH_3$ PET/CT and a research ^{68}Ga-DOTATATE PET/CT. The study group will include adult patients who undergo assessment in Mayo Clinic's CS clinic and have suspected or newly diagnosed CS based upon clinical evaluation. A typical proposed timeline of events for each patient processed through the study is as follows (note exact timeline may vary based on patient appointment schedule):

1) *Up to 4-6 weeks prior to visit:* Patient charts will be reviewed prior to their initial appointment in the CS clinic. After review, the physician head of the CS clinic (LB) will refer candidates that have clinically suspected (7), or newly diagnosed CS and who will be referred for a clinically indicated ^{18}FDG and $^{13}NH_3$ PET/CT to the primary investigator (JB). JB or other designated staff will contact the potential study candidates via phone or email (using a phone/email script) to determine their potential interest in the study. If the patient expresses an interest in the study, a consent form will be sent in advance for their review. Patients may consent remotely if they choose or can also be consented in-person. Potential study subjects will also be notified that they will be contacted during their visit for participation in the study.

2) *Day 1*: During their ^{18}FDG and $^{13}NH_3$ PET/CT assessment, potential study candidates who have not been consented will be approached by the study coordinator to inquire about their participation in the study. If the patient meets all criteria and agrees to participate in the study, then written consent will be obtained at that time.

4) *Day 2 or 3 (1-2 days after ^{18}FDG and $^{13}NH_3$ PET/CT):* Those study candidates who consent to the investigation will then undergo the study ^{68}Ga-DOTATATE PET/CT scan. The patient will be provided with a brief survey at the end of their imaging session which will be conducted by the study coordinator to assess which protocol (if either) they preferred from a patient experience. Note patients will be allowed to complete the ^{68}Ga-DOTATATE PET/CT study within a month of the ^{18}FDG and $^{13}NH_3$ PET/CT exam as long as no intervening immunomodulatory therapy has been administered.

5) Chart and imaging review will be conducted for each of the 15 patients in the study for purposes of drafting the study manuscript.

	Phone Introduction	**Image Visit #1** **^{18}FDG and $^{13}NH_3$ PET/CT Imaging**	**Image Visit #2** **^{68}Ga-DOTATATE PET/CT Imaging**
Phone Introduction	**X**		
Clinically Indicated ^{18}FDG and $^{13}NH_3$ PET/CT		**X**	

Research ^{68}Ga-DOTATATE PET/CT			**X**

3.1 Study Endpoints

1. Assess utilizing both qualitative and quantitative methods the myocardial ^{68}Ga-DOTATATE uptake in patients with and without active CS as determined by ^{18}FDG and $^{13}NH_3$ PET/CT.
2. Determine the concordance and discordance of ^{68}Ga-DOTATATE with ^{18}FDG and $^{13}NH_3$ PET/CT for the presence or absence of CS utilizing ^{18}FDG and $^{13}NH_3$ PET/CT as the "gold-standard" for CS. Determine the sensitivity and specificity of ^{68}Ga-DOTATATE for the detection of CS will be determined.
3. Calculate physician confidence in study interpretation for both ^{68}Ga-DOTATATE and ^{18}FDG and $^{13}NH_3$ PET/CT.
4. Compare patient satisfaction between the ^{18}FDG and $^{13}NH_3$ PET/CT and ^{68}Ga-DOTATATE protocols.
5. Utilize information obtained from the current pilot as a foundation to pursue potentially larger trials.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1) 18 years of age or older
2) Referred for and undergo clinically indicated ^{18}FDG PET/CT scan for CS
3) Have clinically suspected, or newly diagnosed CS
4) Are able to complete both the clinically indicated ^{18}FDG and $^{13}NH_3$ PET/CT and the ^{68}Ga-DOTATATE scan and do so within one month of each other without the introduction of CS directed therapy between the scans

4.2 Exclusion Criteria

1) Pregnant or nursing
2) Unable or unwilling to give consent for ^{68}Ga-DOTATATE PET/CT scan
3) Are on an active immunosuppressive/immunomodulatory therapy

4.3 Early Withdrawal of Subjects

4.3.1 When and How to Withdraw Subjects

The criteria for enrollment must be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be discontinued from the study. A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. If a subject is prematurely discontinued from participation in the study for any reason, at any time, at either the investigator's discretion or the subject's request, an effort must be made to document the reason(s) why a subject fails to return to the study clinic for necessary visits or is discontinued from the study. The primary reason for discontinuing participation in the study must be stated and may include, but is not limited to, one of the following:

- Occurrence of intolerable adverse events
- Withdrawal of consent for imaging by patient
- Noncompliance with protocol, e.g., the patient fails to appear at one or more imaging procedures
- Development of an intercurrent illness, injury, or medical condition likely to interfere with subject safety, the overall assessment, or the required administration of study medication
- Pregnancy
- Development of any condition for which the investigator feels treatment withdrawal is justified
- Termination of the study

Subjects withdrawn from the study will not be replaced, regardless of the reason for withdrawal.

An effort must be made to determine why a subject fails to return for the necessary visits or is dropped from the study.

5 Study Procedures

5.1 Informed Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. The IRB must review the informed consent form used during the informed consent process.

Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB/IEC-approved informed consent form.

(If a procedure is done routinely as standard of care, then it is not study-specific, and it may be done before the consent is signed.)

6 Methods

6.1 PET/CT Imaging

6.1.1 PET/CT Imaging Protocol

A GE Discovery 690XT, Discovery Molecular Insights (DMI) or 710 PET/CT system (GE Healthcare, Waukesha, WI) will be utilized in performing the studies. The imaging system consists of full ring Cerium-doped Lutetium Yttrium Orthosilicate (LYSO) crystals. 128x128 PET matrix size with zoomed 41.9 cm field of view centered over the heart will be used to obtain the PET images. Furthermore, three-dimensional list mode acquisition will be employed. Three-dimensional iterative reconstruction algorithm with time-of-flight correction, CT attenuation, scatter, randoms, normalization, decay and dead time correction will be utilized. Three-dimensional Hanning post-filter with a 10 mm cut-off will also be used.

A 64 slice-spiral CT will be employed with auto exposure control with modulated current in order to maintain consistent noise index (noise index set at 33 with mA range 10-180). For our CT attenuation imaging tube ration is 0.5 s, kV is 120 and pitch is 0.98. Slice thickness is 3.75 mm and slice increment is 3.27 mm. Matrix size is 512 x 21.

As per all of our clinical ^{18}FDG PET/CT CS studies $^{13}NH_3$ will be administered to optimize diagnostic accuracy for CS. This same perfusion map will be used for the ^{68}Ga-DOTATAE imaging portion (no additional ammonia N-13 will be given for the ^{68}Ga-DOTATATE study).

6.1.2 Analysis of PET data

Once the cardiac PET/CT images are obtained they will be assessed for the presence of CS utilizing similar methodologies which were previously published (1,2,24).

Qualitative assessment of ^{18}FDG and $^{13}NH_3$ PET/CT and ^{68}Ga-DOTATATE for each study subject will be made by two different study investigators (JB and AK) who will be blinded to the patient clinical history, laboratory data and any other imaging assessment (including the corresponding CS study-i.e. when reading the ^{68}Ga-DOTATATE study investigators will be blinded to the ^{18}FDG results and vice versa) at the time of interpretation. For both ^{18}FDG and ^{68}Ga-DOTATATE cardiac uptake study investigators will classify the patient into one of four categories of radionuclide uptake: none, diffuse, focal, and focal on diffuse or diffuse. The portions of the myocardium that demonstrate uptake will be documented in accordance with the 17 segment American Heart Association model (28). In concordance with national guidelines(24), ^{18}FDG and ^{68}Ga-DOTATATE examinations will be interpreted simultaneously with $^{13}NH_3$ to allow for assessment of myocardial perfusion. Both ^{18}FDG and ^{68}Ga-DOTATATE studies will then be labeled as positive for CS, negative for CS or inconclusive.

Any discordance between the findings of the two investigators in regards to the presence or absence of CS as well as the extent will be reviewed by additional investigators (GJ or PC) and final determination in regards to classification of the patient will be made.

Semiquantitative determination of radionuclide uptake will be determined by using commercially available software to calculate maximum standard uptake value (SUVmax) of ^{18}FDG and ^{68}Ga-DOTATATE in the heart. This data will be correlated with patient clinical data obtained from the medical record.

The two study investigators (JB and AK) who are reviewing all studies will rank their confidence level for interpretation for each scan on a 5 point scale (1=least confident, 5= most confident). Results will then be compared between the two study modalities.

After completion of both their ^{18}FDG and $^{13}NH_3$ and ^{68}Ga-DOTATATE studies, a study coordinator will administer a patient survey regarding their experience with each protocol which will consist three questions. The first two question will ask the patient to rate the ease of undergoing each study on a 5 point scale (1=easiest, 5=hardest). The third question will ask the patient which study they preferred (^{18}FDG, ^{68}Ga-DOTATATE or equal) with a comment section for why.

7 Statistical Plan

General Considerations

Continuous data (e.g., age) will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max). For each continuous variable, the corresponding mean, median, minimum and maximum will be presented to 1 decimal place and the SD to 2 decimal places, unless otherwise specified.

Categorical variables (e.g., qualitative presence of absence of ^{68}Ga-DOTATATE) will be summarized using counts and percentages. Percentages will be presented to 1 decimal place. Summaries of continuous and categorical data will be presented, as appropriate.

Incomplete/Missing data: Missing data (e.g., dates, post-baseline values) will not be imputed, unless otherwise specified; i.e., all missing values and missing post-baseline values will remain as missing in all statistical analyses and listings, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Additionally, all subject data, including derived variables, will be presented in subject data listings; listings will display all subjects who were randomized or enrolled in the study.

7.1.1 Background Characteristics

7.1.1.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, weight, height and body mass index [BMI]) will be summarized.

7.1.2 Efficacy Analysis

7.1.2.1 Analysis of Primary Efficacy Endpoint

Nominal continuous variables will be represented as the mean +/- SD and categorical variables will be noted as the number and percentage of total. Pearson chi-square test will be utilized to determine statistical significance for continuous variables whereas a Student's two-sample t-test will be implemented to determine statistical significance for continuous variables. Univariate and

multivariate analyses will be performed when relevant. Statistical significance will be set a priori as a p-value less than 0.05. Concordance and discordance of ^{68}Ga-DOTATATE with ^{18}FDG and $^{13}NH_3$ PET/CT for the presence or absence of CS will be calculated and utilizing ^{18}FDG PET/CT as the "gold-standard" for CS, the sensitivity and specificity of ^{68}Ga-DOTATATE for the detection of CS will be determined. Given that this is a pilot study no power calculation will be performed. All statistical analyses will be performed using JMP Pro 9 (SAS Institute INC. Cary, North Carolina).

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

In the following differentiation between medical history and AEs (see below), the term "condition" may include abnormal physical examination findings, symptoms, or diseases.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history.
- Conditions that pertain to efficacy variables of this study, i.e. findings on PET and which are considered pre-existing medical conditions, are not considered AEs unless there is worsening. This also implies that the indication for the imaging procedure and the confirmation of a diagnosis will not be considered as an AE.

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay

- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events will be reported is defined as 24 hours post injection of the radiotracer.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the imaging AE reporting period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study was discontinued
- The reason why the event is classified as serious.

8.3.1 Investigator reporting: notifying the Mayo Clinic IRB

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Mayo Clinic IRB as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

8.4 Safety Monitoring

Subject safety will be monitored continuously by the Investigators. This safety monitoring will include careful assessment and appropriate reporting of adverse events and a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Source documents for the imaging protocol will be kept in a secure location by the principal investigator (Dr. Bois) or his designee.

9.3 Data Management Plan

We will create a database to store patient data. This database will be programmed in REDCap (Research Electronic Data Capture). REDCap is a secure, web-based application with the capacity for direct export to Excel and common statistical packages (SPSS, SAS, Strata, R). REDCap has electronic CRF (eCRF)s, real-time data entry validation, audit trails, user authentication, data logging and encryption. It is HIPAA compliant with mechanisms in place to ensure confidentiality. In addition, logical data checks will be used to assess data quality for mis-entry. Suspect data entries will be flagged for re-review and confirmation by the investigative team. When data are complete and all suspect entries addressed for a time period, the database will be "locked" for analysis. Analysis will use only this final locked version.

9.4 Data Sharing Plan

Clinical data will be exported from REDCap into proper statistical software format for analysis. The final dataset will be provided in proper format to investigators participating in data analysis. The mode of data sharing will be by downloading from REDCap from secure accounts. Data will be secured by electronic safeguards.

10 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to Mayo Clinic Internal Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Study Finances

11.1 Funding Source

CV Prospective Grant (FP00095637)

11.2 Conflict of Interest

The primary investigator and other study investigators have no relevant conflicts of interest.

12 References

1. Lapa C, Reiter T, Kircher M et al. Somatostatin receptor based PET/CT in patients with the suspicion of cardiac sarcoidosis: an initial comparison to cardiac MRI. Oncotarget 2016;7:77807-77814.
2. Gormsen LC, Haraldsen A, Kramer S, Dias AH, Kim WY, Borghammer P. A dual tracer (68)Ga-DOTANOC PET/CT and (18)F-FDG PET/CT pilot study for detection of cardiac sarcoidosis. EJNMMI research 2016;6:52.
3. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation 1978;58:1204-11.
4. Blankstein R, Osborne M, Naya M et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. Journal of the American College of Cardiology 2014;63:329-36.
5. Yazaki Y, Isobe M, Hiroe M et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. The American journal of cardiology 2001;88:1006-10.
6. Cooper LT, Baughman KL, Feldman AM et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. Journal of the American College of Cardiology 2007;50:1914-31.

7. Birnie DH, Sauer WH, Bogun F et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014;11:1305-23.
8. Mana J, Gamez C. Molecular imaging in sarcoidosis. Current opinion in pulmonary medicine 2011;17:325-31.
9. Ohira H, Tsujino I, Yoshinaga K. (1)(8)F-Fluoro-2-deoxyglucose positron emission tomography in cardiac sarcoidosis. European journal of nuclear medicine and molecular imaging 2011;38:1773-83.
10. Youssef G, Leung E, Mylonas I et al. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2012;53:241-8.
11. Ishida Y, Yoshinaga K, Miyagawa M et al. Recommendations for (18)F-fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology recommendations. Annals of nuclear medicine 2014;28:393-403.
12. Bois JP, Chareonthaitawee P. Optimizing radionuclide imaging in the assessment of cardiac sarcoidosis. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2016;23:253-5.
13. Bois JP, Chareonthaitawee P. Continuing evolution in preparation protocols for 18FDG PET assessment of inflammatory or malignant myocardial disease. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2016.
14. Manabe O, Yoshinaga K, Ohira H et al. The effects of 18-h fasting with low-carbohydrate diet preparation on suppressed physiological myocardial (18)F-fluorodeoxyglucose (FDG) uptake and possible minimal effects of unfractionated heparin use in patients with suspected cardiac involvement sarcoidosis. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2016;23:244-52.
15. Nensa F, Tezgah E, Schweins K et al. Evaluation of a low-carbohydrate diet-based preparation protocol without fasting for cardiac PET/MR imaging. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2016.
16. Kyrtatos PG, Constandinou N, Loizides S, Mumtaz T. Improved patient education facilitates adherence to preoperative fasting guidelines. Journal of perioperative practice 2014;24:228-31.
17. Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. American journal of nuclear medicine and molecular imaging 2014;4:426-34.
18. ten Bokum AM, Hofland LJ, de Jong G et al. Immunohistochemical localization of somatostatin receptor sst2A in sarcoid granulomas. European journal of clinical investigation 1999;29:630-6.

19. Owens T CP, and Bois JP. Optimal Patient Preparation For Cardiac FDG PET/CT for Cardiac Sarcoid Imaging. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2017;56:774.
20. Acharya G BJ, Rodriguez-Porcel M, Chareonthaitawee P. Presenting Features in Suspected Cardiac Sarcoid. AHA 2017.
21. Tahara N, Tahara A, Nitta Y et al. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. JACC Cardiovasc Imaging 2010;3:1219-28.
22. Bois JP, Chareonthaitawee P. Radionuclide Imaging in Congestive Heart Failure: Assessment of Viability, Sarcoidosis, and Amyloidosis. Cardiol Clin 2016;34:119-32.
23. Chareonthaitawee P, Bois JP, Gersh BJ. Quantitative Assessment of Myocardial Blood Flow in Cardiac Sarcoidosis: A Potential Next Step in the Further Integration of FDG-PET in Imaging Management? JACC Cardiovasc Imaging 2017;10:168-170.
24. Chareonthaitawee P, Beanlands RS, Chen W et al. Joint SNMMI-ASNC Expert Consensus Document on the Role of (18)F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2017;58:1341-1353.
25. Blauwet LA, Cooper LT. Myocarditis. Prog Cardiovasc Dis 2010;52:274-88.
26. Blauwet LA, Cooper LT. Idiopathic giant cell myocarditis and cardiac sarcoidosis. Heart Fail Rev 2013;18:733-46.
27. Kendti AT JG. Molecular Imaging with Ga68-DOTATATE PET/CT: Neuroendocrine Tumors and Beyond RSNA Conference 2017.
28. Cerqueira MD, Weissman NJ, Dilsizian V et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539-42.