Study to Calculate the Radiation-Absorbed Dose of Technetium-99m Macroaggregated Albumin (^{99m}Tc-MAA) to the Whole Body and Non-Liver Critical Organs (MAApping Study)

Clinical Study Protocol

Study Protocol Number: STX2301

ClinicalTrials.gov Number: NCT05848947

Revision: A, 01Mar2023

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Statistician (CRO)

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	CLINICAL STUDY PROTOCOL SYNOPSIS **Sirtex Medical Study Number: STX2301**
Study Title	Study to Calculate the Radiation-Absorbed Dose of Technetium-99m Macroaggregated Albumin (^{99m}Tc-MAA) to the Whole Body and Non-Liver Critical Organs (MAApping Study)
Identifying Regulatory Numbers	Clinicaltrials.gov – NCT05848947
Study Objective	To evaluate the dosimetry of ^{99m}Tc-MAA after intra-arterial administration to the whole body and non-liver critical organs.
Product Description	Technetium-99m macroaggregated-albumin consists of macroaggregated-albumin particles labeled with technetium-99m (^{99m}Tc), with a size between 10 and 90 microns in diameter. ^{99m}Tc is a gamma emitting radioactive isotope commonly used for diagnostic localization studies.
Study Design	The investigation is a prospective, single center, open label, single-arm study. Patients enrolled in the study will have 3 imaging scans taken after ^{99m}Tc-MAA injection, the final of which will occur between 18 and 24 hours post-injection.
Number of Sites & Subjects	The study will be conducted at one clinical site in the United States and will enroll 5 subjects.
Study Population	The intended population for the study is patients who are undergoing evaluation for SIR-Spheres administration. All subjects enrolled will already be planned to receive ^{99m}Tc-MAA per clinical standard of care, and the decision to offer enrollment in the study will occur only after the decision to deliver ^{99m}Tc-MAA for SIRT planning has already been made.
Endpoints	1. Mean absorbed dose (Gy) for the whole body 2. Mean absorbed dose (Gy) for critical non-liver organs 3. Mean activity (Bq) for the whole body 4. Mean activity (Bq) for critical non-liver organs 5. Effective dose (Gy) for the whole body
Study Eligibility Criteria	Subjects must meet <u>all</u> the following inclusion criteria: 1. Willing, able, and mentally competent to provide written informed consent 2. Age 18 or older at the time of consent 3. Patients who are being evaluated for SIR-Spheres treatment eligibility Subjects must <u>not</u> meet any of the following exclusion criteria: 1. Patients who are contraindicated for SIR-Spheres treatment 2. Patients who are contraindicated for ^{99m}Tc-MAA per the manufacturer's package insert

SIRTeX	**CLINICAL STUDY PROTOCOL SYNOPSIS** **Sirtex Medical Study Number: STX2301**
Study Duration	Enrollment is expected to take approximately 2 months. Each study subject will actively participate in the study through 24-hour follow-up. The overall study duration, from screening the first patient to the final follow-up visit, data analysis, and final report, is expected to be approximately 3 months.
Study Sponsor[a]	Sirtex Medical Inc. 300 Unicorn Park Drive, 2nd Floor Woburn, MA 01801
Study Site	Inland Imaging 5715 N Lidgerwood Spokane, WA 99208
Contract Research Organization (CRO)	BRIGHT Research Partners 730 2nd Avenue South, Suite 500 Minneapolis, MN 55402 [redacted]

[a] Detailed contact information is maintained in a separate Sponsor Contact List managed by the CRO

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1.0 ABBREVIATIONS

The following is a list of abbreviations used in the body of this document. Abbreviations solely used in tables (e.g., table headers) are described in the table footer and are not included below.

Abbreviation	Description
^{99m}Tc	Technetium 99m
^{99m}Tc-MAA	Technetium 99m-labeled macroaggregated albumin
ADL	Activities of daily living
AE	Adverse event
Bq	Becquerel
CFR	Code of federal regulations (U.S.)
(e)CRF	(electronic) case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
EDC	Electronic data capture database
FAS	Full analysis set
FDA	Food and Drug Administration (U.S.)
FUDR	Floxuridine
GCP	Good clinical practice
Gy	Gray
HCC	Hepatocellular carcinoma
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent to treat
keV	Kilo electron-volt
LEAP	Low-energy all purpose
LEHR	Low-energy high resolution
MAA	Macroaggregated albumin
MIRD	Medical Internal Radiation Dose
mSv	Millisievert
NDA	New Drug Application
NMI	Nuclear medicine imaging
OLINDA	Organ Level INternal Dose Assessment
PET	Positron emission tomography

Abbreviation	Description
PI	Principal investigator
ROI	Region of Interest
SAE	Serious adverse event
SIR-Spheres	SIR-Spheres® Y-90 resin microspheres
SIRT	Selective internal radiation therapy
SPECT	Single photon emission computed tomography
VOI	Volume of interest
Y-90	Yttrium-90

2.0 CLINICAL BACKGROUND

The selective internal radiation therapy (SIRT) technique, developed by Gray in the 1980s and 1990s, delivers microspheres containing yttrium-90 (Y-90), a high-energy beta-emitting isotope with no primary gamma emission, directly into the vasculature of hepatic tumors. The goal is to deliver lethal doses of radiation to tumors but sublethal doses to surrounding healthy tissue.

Prior to administration of Y-90 microspheres, an evaluation of arterial flow at the implantation site is made using Technetium Tc 99m-labeled macroaggregated albumin (^{99m}Tc-MAA); this is often referred to as a "lung shunt" study or mapping procedure. After intra-arterial administration of ^{99m}Tc-MAA, the patient is imaged via planar, single photon emission computed tomography (SPECT), or SPECT/CT. The patient-specific image is analyzed and used in calculating the patient-specific radiation dose for implant per the microsphere instructions for use.

SIR-Spheres® Y-90 resin microspheres (SIR-Spheres) were approved by the Food and Drug Administration (FDA) as a Class III medical device in 2002 for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intrahepatic artery chemotherapy of floxuridine (FUDR). TheraSphere™ Y-90 glass microspheres (Boston Scientific) were approved by the FDA as a Class III medical device in 2021 for the treatment of patients with hepatocellular carcinoma (HCC). At present, the DOORwaY90 study (IDE G200352) is evaluating use of SIR-Spheres Y-90 for the treatment of HCC.

While commonly used for mapping procedures prior to SIRT, ^{99m}Tc-MAA is labeled for intravascular administration but not intra-arterial administration. The purpose of this study is to fulfill an FDA request for a dosimetry study to evaluate the radiation-absorbed dose of ^{99m}Tc-MAA to the whole body and non-liver critical organs. Study data will support radiation risks described in SIR-Spheres Y-90 product labeling.

3.0 REGULATORY CLASSIFICATION

This clinical investigation of a marketed drug is exempt from the Investigational New Drug (IND) requirements as all of the criteria for an exemption in § 312.2(b) are met:

Requirement for exemption	Comments
The drug product is lawfully marketed in the United States.	^{99m}Tc-MAA is lawfully marketed in the United States. ^{99m}Tc-MAA is part of the current clinical standard of care for preparation of SIRT procedures and has been in commercial use since 1976.
The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.	The investigation will not support a new indication or change in labeling for ^{99m}Tc-MAA.

Requirement for exemption	Comments
In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.	The investigation is not intended to change advertising for ^{99m}Tc-MAA.
The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).	The risk associated with the use of ^{99m}Tc-MAA will not be significantly increased nor will the acceptability of risk be decreased due to the low levels of radiation to be absorbed by non-target organs as well as low-level whole-body exposure, all of which are expected to be < 15mGy (Kappadath). This level of exposure is similar to that seen when MAA is delivered for pulmonary imaging in standard practice according to its labeling. Current standard practice for radioembolization treatment planning makes use of nuclear medicine imaging (NMI) of 99mTc-MAA arterial distributions for the assessment of lung shunting and extrahepatic uptake; 99mTc-MAA will be administered under the operation of an authorized user per 10 CFR 35.290 as stated in the study protocol. Subjects in the investigation are already intended to receive 99mTc-MAA for SIRT planning regardless of their enrollment, and thus the study does not involve the use of 99mTc-MAA or any other drug apart from their already intended treatment (Gates). In this context, the use of 99mTc-MAA is associated with improved quality of subsequent SIRT procedures, thus reducing the overall risk to the subject. As noted above, all subjects enrolled in the study would already be receiving MAA as SIRT candidates; hence, the only study-specific procedure is SPECT-CT, which will be performed for MAA dosimetry. The radiation exposure from diagnostic CT procedures is estimated to be in the range of 1 to 10 mSv, with an abdominal CT effective dose of 8 mSv (McCollough). In assessing the associated risk, McCollough *et al.* conclude that there is no convincing epidemiological evidence of increased cancer incidence or mortality at doses less than 100 mSv.
The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).	The investigation will be conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50), as stated in the study protocol.

Requirement for exemption	Comments
The investigation is conducted in compliance with the requirements of §312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).	The investigation will be conducted in compliance with the requirements of §312.7, as the investigation is not intended to promote or commercialize ^{99m}Tc-MAA with updated labeling. • The objective of the investigation is solely to address an FDA request to evaluate the dosimetry of ^{99m}Tc-MAA in the context of preparation for SIRT procedures. • The sponsor of the investigation has no financial or other interest in ^{99m}Tc-MAA or in its promotion or commercialization. The use of ^{99m}Tc-MAA in this context is part of the current clinical standard of care for preparation for SIRT procedures.

4.0 ^{99M}TC MAA DESCRIPTION

^{99m}Tc-MAA is lawfully marketed in the United States. Product labeling is provided with the commercial dose of ^{99m}Tc-MAA. The macroaggregated albumin (MAA) particles are used to simulate the distribution of the therapeutic SIR-Spheres resin microspheres prior to administration of the therapy. MAA is obtained by heat denaturation of stannous chloride treated human serum albumin under controlled conditions. MAA is provided to the radiopharmacy as 10- or 15-mL (depending on the manufacturer) vials containing white lyophilized powder. Upon radiolabeling with sodium pertechnetate ^{99m}Tc injection solution, the stannous reduced ^{99m}Tc binds to the aggregated albumin. The kits do not contain any bacteriostatic agents; however, the rubber septum should be cleaned with alcohol swabs or bacteriostatic agents following the removal of the plastic cap.

Volume of the vials, maximum ^{99m}Tc activity, amounts of MAA, human serum albumin, total tin (as SnCl2 · 2H2O), stannous chloride, sodium chloride and pH adjustment agents may vary depending on the manufacturer.

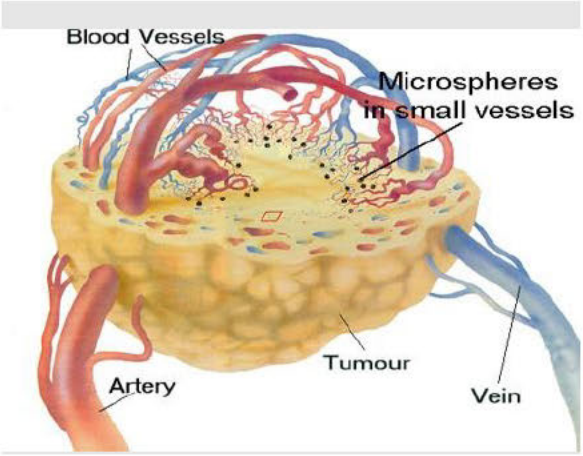
Typically, individual syringes of 3-5 mCi of ^{99m}Tc-MAA are provided by the radiopharmacy to client sites to be used in the mapping procedure.

^{99m}Tc decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for gamma SPECT imaging is present with an abundance of 89.07% and energy of 140.5 keV.

4.1 Principle of Operation / Mechanism

During SIRT, radioactive Y-90 microspheres are intra-arterially infused proximal to the tumor target to provide direct irradiation of tissue and destruction of the microvascular bed (**Figure 1**).

Figure 1. SIR-Spheres Selectively Delivered to Liver Tumor



During the mapping procedure in preparation for SIRT, ^{99m}Tc-MAA is administered intra-arterially from the intended SIRT treatment location. The infused MAA particles aggregate in the microvasculature of the tumor and liver tissue. The patient is imaged using SPECT/CT imaging to count the gamma emission from the ^{99m}Tc. This serves as a simulated therapeutic procedure that provides information for the treating physician in order to optimize dosimetric predictions for the therapy and minimize potential for over administration of activity/dose to non-targeted areas.

5.0 OBJECTIVE

To evaluate the dosimetry of ^{99m}Tc-MAA after intra-arterial administration to the whole body and non-liver critical organs.

6.0 ENDPOINTS

6.1 Primary Endpoints

The primary endpoints for this study are as follows:

1. Mean absorbed dose (Gy) for the whole body
2. Mean absorbed dose (Gy) for critical non-liver organs
3. Mean activity (Bq) for the whole body
4. Mean activity (Bq) for critical non-liver organs
5. Effective dose (Gy) for the whole body

6.2 Rationale for Study Endpoints

The study endpoints are selected to provide an assessment of radiation activity and dose over time, with primary interest in dose to critical non-liver organs and the whole body. The endpoints will therefore provide useful information in understanding the behavior of ^{99m}Tc-MAA in patients undergoing planning for a subsequent SIRT procedure.

7.0 STUDY DESIGN

7.1 Overall Design

The investigation is a prospective, single center, open label, single-arm study. Patients enrolled in the study will have 3 imaging scans taken after ^{99m}Tc-MAA injection, the final of which will occur between 18 and 24 hours post-injection.

7.2 Number of Sites & Subjects

The study will be conducted at one clinical site in the United States and will enroll 5 subjects.

7.3 Study Population

The intended population for the study is patients who are undergoing ^{99m}Tc-MAA injection as evaluation for subsequent SIRT. All subjects enrolled will already be planned to receive ^{99m}Tc-MAA per clinical standard of care, and the decision to offer enrollment in the study will occur only after the decision to deliver ^{99m}Tc-MAA for SIRT planning has already been made.

7.4 Study Duration

Enrollment is expected to take approximately 2 months. Each study subject will actively participate in the study through 24-hour follow-up. The overall study duration, from screening the first patient to the final follow-up visit, data analysis, and final report, is expected to be approximately 3 months.

7.5 Subject Eligibility Criteria

7.5.1 Inclusion Criteria

Subjects must meet all the following inclusion criteria:

1. Willing, able, and mentally competent to provide written informed consent
2. Age 18 or older at the time of consent
3. Patients who are being evaluated for SIR-Spheres treatment eligibility

7.5.2 Exclusion Criteria

Subjects must not meet the following exclusion criteria:

1. Patients who are contraindicated for SIR-Spheres treatment
2. Patients who are contraindicated for ^{99m}Tc-MAA per the manufacturer's package insert

8.0 STUDY METHODOLOGY

Study assessments and data collection points are visually represented in **Figure 1** and **Table 1** and are described below. Study procedures should be followed as they have been designed to address any known or foreseeable factors that may compromise the outcome of the clinical study or the interpretation of results (e.g., subject baseline characteristics, concomitant

medication, the use of medical devices, and subject-related factors such as age, gender, or lifestyle) and methods for addressing these factors (e.g., subject selection, statistical analysis).

Figure 1: Study Flow Diagram

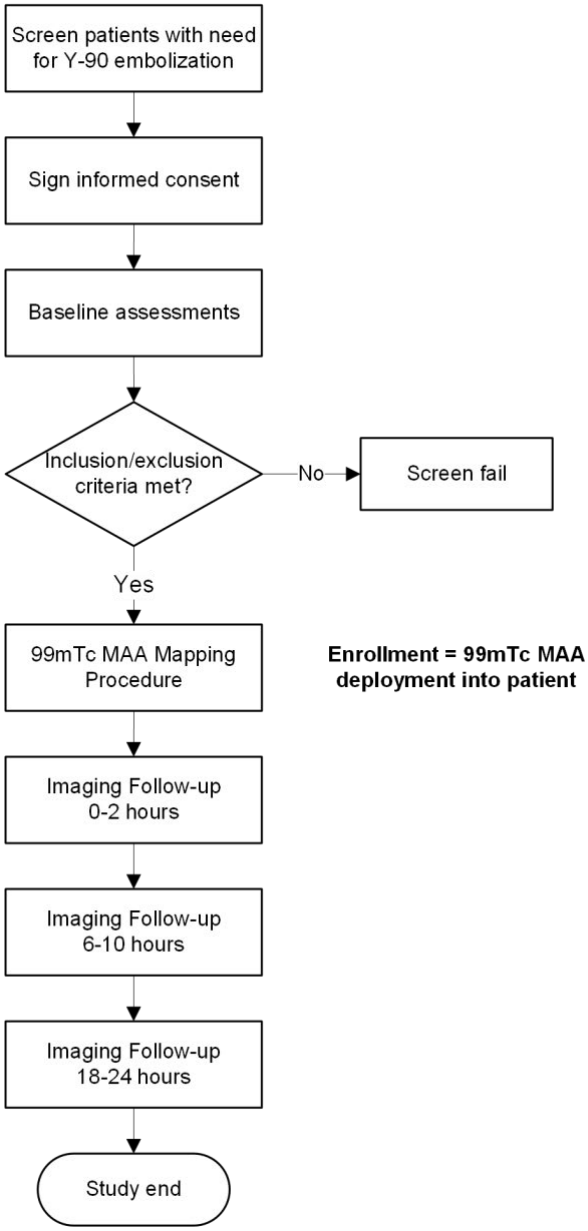


Table 1: Schedule of Study Activities

Assessment	Study Visit				
	Screening	Procedure	0-2 hours	6-10 hours	18-24 hours
Eligibility criteria	X				
Informed consent	X				
Demographics/medical history	X				
99mTc-MAA infusion		X			
Imaging (SPECT/CT)[1]			X	X	X
Adverse event assessment		X	X	X	X
[1]Used for quantitative analyses					

8.1 Screening Visit

The study team will screen patients for the study. Screening is defined as the process of reviewing a patient's medical records against the study eligibility (inclusion and exclusion) criteria to determine if the patient is potentially eligible to enroll in the study. It is expected that the medical records will contain adequate information to determine if a patient meets most of these criteria. If the investigator (or designee) determines the patient meets standard of care inclusion and exclusion criteria, they can be consented for study participation; informed consent may be obtained prior to or at the time of the procedure.

8.1.1 Informed Consent Process

Prior to enrolling patients in this study, the site will be required to have an Institutional Review Board (IRB) approved informed consent form (ICF). To ensure compliance with informed consent requirements, the contract research organization (CRO) must review any modifications made to the sponsor's template ICF prior to IRB submission.

Written informed consent will be obtained from the patient prior to the subject's participation in the study. The investigator (or authorized designee) will explain the nature of the planned treatment and objectives of the study to the patient, along with any costs to the subject and payments for participation. The investigator will allow adequate time for the patient to read and review the consent form and to ask questions. When the investigator has reasonable assurance that the patient has an acceptable level of comprehension and the patient voluntarily agrees to participate, the patient and the investigator (or authorized designee) will sign and date the ICF.

The site will retain the original signed ICF in the subject's study records and will provide a copy of the ICF to the subject. The site will document the consent process (e.g., that the subject was consented, the date on which the consent was obtained, that a copy of the signed ICF was given to the subject, and that no study procedures were conducted prior to obtaining consent) in the subject's medical records.

Subjects will be informed of any new information that may make him/her change their mind about staying in the study. Subjects may be asked to sign a new ICF if this occurs.

8.1.2 Vulnerable Population

To preserve the ethical integrity of this study, the sponsor does not intend to enroll vulnerable subject populations (e.g., incarcerated persons or adults with severe cognitive challenges) in this study since such populations may be coerced or compelled to participate in a clinical study without a full understanding or against their will these subjects should be excluded (in consideration of 21 CFR 56.111(b)).

8.2 Point of Enrollment & Numbering of Study Subjects

A patient will be considered enrolled as a study subject when the investigator deploys any release of the ^{99m}Tc-MAA into the patient. The lowest available subject number will be assigned, progressing sequentially for each enrolled subject thereafter.

8.3 Procedure Visit

The intra-hepatic ^{99m}Tc-MAA infusion and scan will be conducted by a trained interventional radiologist; steps are briefly outlined below.

- Establish the anticipated treatment volume using angiography assessed by imaging (e.g., cone beam CT)
- Select the hepatic artery with a microcatheter corresponding to the anatomical area of interest, and in a position that will simulate treatment with SIR-Spheres Y-90 resin microspheres
- Attach a syringe containing 150 MBq of ^{99m}Tc-MAA and infuse it into the hepatic artery via the microcatheter
- Flush and remove the microcatheter
- Transfer the patient to nuclear medicine for SPECT/CT imaging within 2 hours

An adverse event (AE) assessment will be performed and the results will be recorded on the AE case report form (CRF).

8.4 Subject Follow-Up (3 timepoints: 0-2 hours, 6-10 hours & 18-24 hours)

Subjects will be evaluated at the three specified imaging timepoints post- ^{99m}Tc-MAA injection. The assessments described below will be performed at each timepoint, and results will be recorded on the relevant eCRFs.

- SPECT/CT in accordance with the acquisition protocol as described in **Section 8.4.1**
- Adverse event assessment

At the conclusion of this follow-up subjects will exit from this study via completion of the Study Completion CRF. Subjects will continue to be followed by their physician per usual care.

8.4.1 SPECT/CT Acquisition Protocol

The SPECT/CT acquisition protocol outlined below ensures quantitative imaging. To determine the image calibration factor (i.e., cps/MBq), a cylindrical phantom (Jaszczak phantom), will be filled with a uniform distribution of ^{99m}Tc (target activity of 400 MBq). The filling volume will be determined by weighing (i.e., difference between filled and empty phantom).

The reconstructed cylindrical phantom data will be used to determine a setup-specific image calibration factor for ^{99m}Tc: $ICF = \frac{C}{T \cdot A_{calibrator}}$ where C is the counts in the reconstructed image within a cylindrical volume of interest (VOI) corresponding to 130% of the radius and 120% of the height of the phantom, T is the acquisition duration (unit: s), and $A_{Calibrator}$ (unit: Bq) is the activity dispensed

CT Parameters	Good quality low noise (e.g., 130 kV, 30 mAs)
SPECT Acquisition Parameters	360 scan range, 120 projections, 20 to 30 seconds per stop
Collimator	LEAP or LEHR
Primary Energy Window	126-154 keV (e.g., 140 ± 10%)
Scatter Energy Window	98-126 keV (e.g., 112 ± 12.5%)
Reconstructions	OSEM3D with 2 iterations, 16 subsets
Corrections	AC + SC + RR (optional)
Field of View	Entire liver, entire lungs, superior bowel
Transverse Image Array Size	128 x 128
Abbreviations: kiloelectronvolt (keV), low-energy all purpose (LEAP), low-energy high resolution (LEHR), milliampere-seconds (mAs)	

8.4.2 Imaging Analysis

Quantitative gamma SPECT/CT will be performed over the chest and abdomen of the patient at specified timepoints after intra-arterial administration of ^{99m}Tc-MAA. Absorbed dose in units of mGy/GBq for each organ of interest and total absorbed dose within the imaged area will be calculated using a 510(k) cleared software product. Mean absorbed doses ± standard deviation for each region of interest will be calculated for the study population.

8.5 Early Withdrawal/Premature Discontinuation of Subjects

Subjects may be withdrawn early from the study for several reasons including:

- Subject death
- Subject request for withdrawal (withdrawal of consent)

- Adverse event
- Investigator decision

If a subject is withdrawn from the study early, a Study Completion CRF must be completed to describe the reason for early withdrawal. In situations where study withdrawal is due to an adverse event, subjects will be followed until resolution of the adverse event or determination that the subject's condition is stable.

If a subject chooses to withdraw from the study and also withdraws consent for disclosure of further information, no further study assessments should be performed and no additional data collected. The sponsor may retain and continue to use any data collected prior to the withdrawal of consent.

8.5.1 Subject Replacement

If a subject is withdrawn prior to the 24-hour follow-up, they will be replaced. Subject numbering will proceed as described in **Section 8.2**.

9.0 STATISTICAL METHODS

9.1 Analysis Data Sets

The primary analysis will consist of all available data on all subjects enrolled, referred to in International Conference on Harmonisation (ICH) E9 Statistical Principles for Clinical Trials as the full analysis set. As the study is a treatment-only, single arm design, comparisons between treatment and control groups are not pertinent, and summaries of results will principally be presented for the entire study population.

9.2 General Principles

Continuous data will be summarized using the following descriptive statistics: mean, standard deviation, median, and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. For events that can occur more than once in a single subject, such as AEs, the percentage will be based on the number of subjects experiencing the event; both subject and event counts will be reported.

All statistical analyses will be performed using SAS (version 9.4 or higher, SAS Institute Inc. Cary, NC), R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical or graphical software.

9.3 Analysis of Primary Endpoints

The primary endpoints are defined in **Section 6.1** and will be presented descriptively under the general principles cited above. Summary statistics for each endpoint will be reported at each of the three timepoints at which they are measured, thereby obtaining activity (GBq) and dose (Gy) over time related to ^{99m}Tc-MAA as part of SIRT planning. As the study is nonrandomized, summary statistics of primary interest are those for the enrolled population as a whole and

evaluation of subgroups is not planned *a priori* and no hypothesis testing against predefined null hypotheses or between subgroups is expected.

9.4 Safety Analysis

An overall summary of severe adverse events (AEs, grade ≥3) that occur over the 24-hour period of the study will be presented. The summary will include the number and percentage of subjects with at least one AE and the total number of AEs. Complete subject listings of all site-reported AEs will be provided.

AEs will additionally be classified according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 terms, summarized by severity, relationship to the ^{m99}Tc-MAA study, outcome, and seriousness. Serious adverse events (SAEs) will be summarized according to severity and relationship. Multiple occurrences of the same AE are counted once at the maximum grade.

10.0 MEASURES TO AVOID & MINIMIZE BIAS

The study has several measures that have been implemented to avoid and minimize bias, including use of an independent CRO for study operations management, monitoring, and data management.

11.0 BENEFITS & RISK ANALYSIS

11.1 Potential Benefits of Study Participation

There are no guaranteed benefits from participation in this study. There is no obligation for a patient to take part in this study. As an alternative to participation, patients may choose to receive standard of care mapping procedures while being evaluated for SIR-Spheres eligibility.

11.2 Potential Risks Associated with Study Participation

Risks associated with ^{99m}Tc-MAA mapping procedure will be listed in the site's procedure consent form used per their standard of care.

Two non-standard of care SPECT/CT scans will be conducted for this study, which involves additional exposure to ionizing radiation. Ionizing radiation exposure risks include a very small increase in the likelihood that a person exposed to radiation will develop cancer later in life. However, the doses used in CT examinations are 10 to 100 times lower than the dose levels that have been reported to increase the risk of cancer (McCollough).

11.3 Methods to Minimize Risks

^{99m}Tc-MAA is a well-known and well characterized radiopharmaceutical. Only authorized users with training and licensure per 10 CFR 35.290 can order ^{99m}Tc as a radioisotope to be used for imaging and localization.

In addition, risks will be further minimized through careful subject screening and selection, training of investigators and study staff, adherence to the scheduled assessments, and regular monitoring visits.

12.0 ADVERSE EVENTS

12.1 Adverse Event Definitions

Adverse events (AEs) will be adjudicated for severity, seriousness, and for relatedness to the ^{m99}Tc-MAA drug and ^{m99}Tc-MAA procedure. Refer to **Section 14.0** for AE definitions.

12.2 Adverse Event Collection & Documentation

Collection of AEs will start on the day of the procedure for enrolled subjects and will be assessed and reported throughout the study. Investigators must obtain all information available to determine the seriousness, relatedness, and outcome of the adverse event. All AEs will be followed until resolution or investigator determination that the subject's condition is stable.

All reported AEs will be documented on the AE eCRF. Copies of de-identified source documentation that contain significant information related to the event (e.g., progress notes, consultations, nurse's notes, operative reports, subject summaries) may be requested by the sponsor and CRO as needed for evaluation.

The following are not considered AEs for this study:

- Any condition that is recorded as pre-existing on the Baseline eCRF, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.
- Planned hospitalization for pre-existing conditions or a procedure required by the protocol, without serious deterioration in health.
- AEs arising from vascular access (e.g., hematoma, pseudoaneurysm, etc.), catheter selection (e.g., rupture, dissection, thrombosis).

12.3 Adverse Event Reporting Timeframes

The investigator is responsible for reporting SAEs to the IRB in accordance with the IRB's procedures.

- **Investigator Report:** If a subject experiences a reportable AE the investigator must notify the sponsor/CRO and the reviewing IRB immediately.
- **Postmarketing safety reports:** Applicants (individual or corporate entity that holds an NDA) are required to submit post-marketing safety reports to the FDA for human drug products with approved NDAs (§ 314.80).

12.4 Adverse Event Severity

The severity of an AE is a qualitative judgment of the degree of intensity, as determined by the investigator. The severity of the AE should be evaluated according to CTCAE v5.0. In the event a new version is released, this study will continue to use CTCAE v5.0. Refer to the severity of the AE – CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
    - Instrumental ADL: Preparing meals, shopping for groceries and clothes, using the telephone, managing money, etc.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
    - Self-Care ADL: Bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

The assessment of severity should be made independent of the relatedness to the device and procedure or the seriousness of the event. CTCAE grading information is available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

12.5 Adverse Event Relatedness

The investigator will assess the relatedness of the AE to ^{99m}Tc-MAA drug and the ^{99m}Tc-MAA mapping procedure using the categories listed below (see **Section 14.0** for definitions):

- Definitely
- Probably
- Possibly
- Unlikely
- Not Related

13.0 ADMINISTRATIVE PROCEDURES

13.1 Records & Reports

13.1.1 Case Report Forms

Worksheets will be used to collect subject data that is not readily available from the source documentation. An electronic data capture (EDC) system will be used to collect study-required data on eCRFs. The principal investigator (PI) at the site is responsible for ensuring eCRFs are accurate and completed in a reasonable timeframe. The PI is required to review and approve the eCRF on the appropriate page(s) to verify the completeness, accuracy, and authenticity of the recorded data.

13.1.2 Sponsor / CRO Study Records

The sponsor and CRO are responsible for maintaining study records and reports per applicable ICH Good Clinical Practices (GCP), FDA regulations, and applicable standard operating procedures and study-specific plans (e.g., Monitoring Plan, Data Management Plan, Training Plan, and Statistical Analysis Plan).

13.1.3 Investigator Study Records

The investigator will securely maintain the following accurate, complete, and current records relating to their participation in the study as follows:

- All essential correspondence that pertains to the investigation.
- Records of each subject's case history and exposure to ^{99m}Tc-MAA during the study. Case histories include the CRFs and supporting data including, for example, signed and dated ICFs and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records will include:
    - Documents evidencing the informed consent process. The case history of each subject will document that informed consent was obtained at the appropriate time.
    - All relevant observations, including records concerning AEs (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
    - A record of the exposure of each subject to the ^{99m}Tc-MAA, including the date and time of use.
- The protocol, with documents showing the dates and reasons for each deviation from the protocol.
- Signed investigator agreements, financial disclosure agreements, investigator protocol signature pages, and curriculum vitae.
- IRB approval documents including approval of the protocol, protocol amendments, and ICF.

13.1.4 Investigator Reporting Requirements

Investigator reporting requirements are described in **Table 2** below.

Table 2: Investigator Reporting Requirements

Report	Submitted to	Description
Serious Adverse Events (SAE)	Sponsor/CRO & IRB	An investigator must immediately report to the sponsor any serious adverse event. Report to the IRB per IRB reporting requirements.
Serious and Unexpected Suspected Adverse Reaction	NDA holder	NDA holder of ^{99m}Tc-MAA to submit postmarketing report to FDA (CFR 310.305, 314.80)
Withdrawal of IRB approval	Sponsor/CRO	Notification within 5 working days of withdrawal.
Progress Report	Sponsor/CRO & IRB	Periodic report detailing the progress of the study, occurring at least annually.
Deviations from protocol (CFR 812.150)	Sponsor/CRO & IRB	**Emergency Use:** Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). **Other:** If the deviation affects scientific soundness of the study or the rights, safety, or welfare of the subject (and is not an emergency), prior approval must be obtained from sponsor the reviewing IRB, and FDA when required.
Failure to obtain informed consent	Sponsor/CRO & IRB	Notification within 5 working days
Final Report	IRB	Submitted within 3 months after termination or completion of the investigation.

13.1.5 Record Storage & Retention

Refer to the Clinical Trial Agreement for trial data storage, access, and retention requirements.

13.2 Data Management

Correction of missing or unclear data will be requested as necessary throughout the study. The CRO may request additional information including source documentation as needed. The CRO will also be responsible for confirming the overall integrity of the data. Refer to the study Data Management Plan for more details.

13.3 Product Accountability

Product accountability procedures are not required because ^{99m}Tc-MAA is a commercially available product.

13.4 Site Qualification & Selection

The sponsor and/or CRO will assess the potential site to ensure the investigators and his/her staff meet the following criteria at minimum:

- The site has an interventional radiologist that can act as a principal investigator.
- The investigators are qualified by experience and training.
- The site has the appropriate ^{99m}Tc-MAA SPECT/CT imaging equipment.
- The site has adequate research support staff with the availability to fulfill the clinical study requirements specified in the protocol.
- The investigators are not on the FDA disqualified or debarred list.

13.5 Site Training

Training of the clinical site personnel will be the responsibility of the study sponsor and the CRO. Site personnel will be trained per the study-specific Training Plan. All site personnel will undergo training prior to performing any study-related procedures. All training will be documented. Existing site personnel who have been delegated new tasks and new site personnel will undergo training as designated in the Training Plan.

13.6 Site Monitoring

This clinical study will be monitored according to a study-specific Monitoring Plan that complies with GCP. Monitors will assess for appropriate study conduct and data integrity, including review of eCRFs and parity checks with the source documentation, worksheets, and hospital charts. Periodic site visits will be conducted (either on-site or remotely), including a site initiation visit, routine monitoring visits, and a study closeout visit upon completion of the study. At a minimum, the ICF and the ICF process, imaging timepoint data, and AE data will be 100% monitored and compared to source documentation. Monitoring will include comparison of eCRFs to source documentation for accuracy and appropriateness, and review for unreported AEs.

13.7 Institutional Review Board (IRB)

The CRO must have documented IRB approval for the protocol and the site-specific ICF prior to site activation to enroll subjects. The IRB approval documentation should be signed by the IRB chairperson and clearly identify the study (i.e., study number, protocol title, and version), the documents that were approved (e.g., protocol, ICF), and the date of IRB approval. The site will not be activated until a copy of written and dated IRB approval has been received by the CRO and other applicable study activation requirements are complete.

The site must submit any protocol or ICF amendments to the IRB and is required to forward a copy of the written approval to the CRO. An IRB approval of the amended document(s) must be obtained before implementation and before new subjects are consented to participate in the study using the amended ICF, if applicable. The IRB should also be informed of any event likely

to affect the safety of subjects or the conduct of the study. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

The ICF must be reviewed by the CRO before it is submitted to the IRB for approval.

13.8 Protocol Deviations

A protocol deviation is defined as a circumstance in which the investigator or other site personnel did not conduct the trial according to the protocol, applicable laws/regulations, or any study agreements (e.g., Clinical Trial Agreement or Investigator Agreement).

Every attempt will be made to adhere to the protocol. However, should an investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice will be given to the sponsor or CRO and IRB as soon as possible, but no more than 5 working days from the date the emergency occurred. Except for an emergent circumstance, prior approval from the sponsor, the IRB, and the FDA (when required) is required for any change in, or deviation from, the protocol, as such changes may affect the scientific soundness of the protocol or the rights, safety, and welfare of study subjects.

Protocol deviations will be documented on the Protocol Deviation eCRF. Deviations are reportable to the IRB during the annual reporting process, unless otherwise directed by the governing IRB requirements.

Repeated protocol deviations will be closely monitored by the CRO/sponsor. If excessive deviations or a failure to reduce deviations is noted, the sponsor reserves the right to suspend study enrollment or terminate the site from the study until a sufficient system is in place at the site to reduce further deviations (21 CFR 812.46(a)).

13.9 Protocol Amendments

Changes to the protocol must be documented in a formal protocol amendment prior to implementation in the study. Amendments to the protocol will be initiated by the sponsor or CRO and must be approved by the IRB prior to implementation at the site.

13.10 Study Suspension or Termination

No formal statistical rule for early termination of this study for insufficient effectiveness of the study drug is defined.

The sponsor reserves the right to terminate or suspend the study for valid scientific reasons or reasons related to the protection of subjects (e.g., the discovery of an unexpected, significant, or unacceptable risk to the subjects). The sponsor also reserves the right to terminate the study for business reasons. Refer to the Clinical Trial Agreement for specific information regarding study termination (by IRB withdrawal of approval, by principal investigator (PI), or by sponsor).

If the study is terminated prematurely or suspended, the sponsor will promptly inform the Investigator of the termination or suspension and the reason(s). The IRB will also be informed,

either by the sponsor or investigator, and provided with the reasons(s) for the termination or suspension. Regulatory authorities will be informed, as required.

The IRB may choose to discontinue the study for which they granted approval if the research study is not conducted in accordance with the IRB's requirements or the research study indicates unexpected serious harm to subjects.

13.11 Subject Confidentiality

All information and data sent to the CRO concerning a subject or their participation in this study will be considered confidential. The sponsor, CRO, monitors, IRB, and regulatory representatives will have access to these confidential files and have the right to inspect and copy all records pertinent to this study for data verification. All data used in the analysis and reporting of this study will be without identifiable references to a subject. Subject names and contact information will be available to the sponsor, CRO, and monitors during review of medical records. Subject names may be available as required for review of study-related radiographic images and source documentation. This information will be treated with adherence to professional standards of confidentiality. In addition, upon regulatory request, subject records shall be provided to regulatory agencies. Efforts will be made to de-identify information whenever possible.

13.12 Audits & Inspections

Investigators and study sites are required to permit study-related monitoring, audits, IRB review, and regulatory inspection(s) and provide direct access to source data/documents.

13.13 Statements of Compliance

This study is to be conducted in compliance with the study protocol and in accordance with ethical principles that have their origin in the Declaration of Helsinki, as defined in the following U.S. and international standards for good clinical practice:

- ICH Guideline for Good Clinical Practice E6 (R2) (2016)
- U.S. Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 11, 50, 54 and 56 and 812) and HIPAA (45 CFR 164.508)

13.14 Finance & Agreements

Refer to the Clinical Trial Agreement for a description of how the clinical investigation is financed and the agreement between the sponsor and the site.

13.15 Publications & Public Disclosure

Refer to the Clinical Trial Agreement for publications and public disclosure requirements and conditions.

13.16 Study Contacts

Refer to the Study Contact List for detailed contact information, including names, telephone numbers, and email addresses.

14.0 DEFINITIONS

Adverse drug reaction (ADR): In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (i.e., the relationship cannot be ruled out). (ICH E6 (R2), 1.1)

- Note regarding marketed medicinal products: A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse event (AE): 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 AE 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 related to the medicinal (investigational) product. (ICH E6 (R2), 1.2)

Serious adverse event (SAE) or serious suspected adverse reaction: An AE 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 participant 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. (U.S. FDA 21 CFR 312.32(a))

Suspected adverse reaction (SAR): Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting,

"reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. (U.S. FDA 21 CFR 312.32(a))

Unexpected: An adverse event or adverse drug reaction is considered “unexpected” if the nature or severity of the event is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational drug or package insert/summary of product characteristics for an approved drug). (U.S. FDA 21 CFR 312.32(a))

- Note: A suspected unexpected serious adverse reaction may be referred to as a SUSAR.

15.0 REFERENCES

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16.0 REVISION HISTORY

Rev.	Description of Changes	DCO #	Effective Date
A	Initial release.	2023-02-004	3/1/2023