Boston Scientific

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TheraSphere Post-Approval Study

Study Reference Number: S2494

CLINICAL INVESTIGATION PLAN

Sponsored By:

Boston Scientific Corporation

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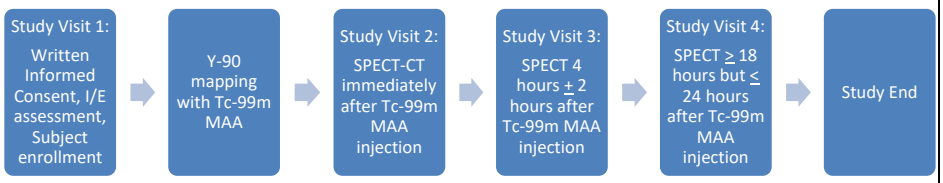
Vendors/Labs/External Organizations	A list of vendors/laboratories/external organizations involved in the trial is maintained by the sponsor. A complete listing of applicable vendors will be provided to clinical study sites.

Original Release: August 17, 2021

Current Version: October 27, 2022

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	**17 AUG 2021**	**92120219, Rev F**	**N/A**	**Initial Release**	**N/A**
B	**27 OCT 2022**	**92120219, Rev F**	• **2. Protocol synopsis** • **4. Introduction** • **6. Study Objective** • **7. Study Design** • **8. Subject Selection** • **10. Study Methods** • **14. Compliance** • **23. Abbreviations and Definitions**	• **Removed reference to the TheraSphere IFU** • **Removed reference to uploading images to Imaging Portal** • **Corrected 21 CRF 50 and 56 to 21 CFR 50 and 56** • **Removed abbreviations and definitions that do not appear in the text**	• **Updates to support study enrollment by allowing inclusion of all patients receiving Tc-99m MAA infusion to determine eligibility for TheraSphere treatment. No impact on study results is expected from this update.** • **Updates to reflect change in image processing: analysis is being performed at study site instead of at a core lab, no upload of images required.** • **Administrative**

2. Protocol Synopsis

Patient Exposure Study	
Study Objective(s)	Primary Objective: to calculate the radiation-absorbed dose of Technetium-99m macroaggregated albumin (Tc-99m MAA) to the whole body and to potential irradiated non-liver critical organs.
Patient Population	Patients who are being evaluated for TheraSphere administration.
Study Product	Tc-99m macroaggregated albumin
Study Design	Post-market prospective, single-arm, open-label, observational study. Patients will be required to provide written informed consent prior to any study procedures being conducted. Patients who provide written informed consent, fulfill all the inclusion criteria and meet none of the exclusion criteria will be considered enrolled in the study. Patients who are enrolled in the study will have 3 images taken after Tc-99m MAA injection, with the final image occurring between 18 and 24 hours after Tc-99m MAA injection. 
Planned Number of Patients	A total of five patients will be enrolled in the study.
Planned Number of Sites / Countries	The study will be conducted at up to three clinical study sites in the US.

Patient Exposure Study	
Primary Endpoints	Mean absorbed dose (Gy) and activity (Bq) will be summarized for the whole body and for critical non-liver organs (including whole body effective dose).
Follow-up Schedule	At a minimum, all patients will be evaluated at the following timepoints: • Immediately following Tc-99m MAA injection • 4 hours ± 2 hours after Tc-99m MAA injection • ≥ 18 hours after Tc-99m MAA injection but ≤ 24 hours after Tc-99m MAA injection At each evaluation timepoint, the following images will be performed: • Immediately following Tc-99m MAA injection: Single Photon Emission Computed Tomography in conjunction with Computed Tomography (SPECT-CT) • All other images: Single Photon Emission Computed Tomography (SPECT) The start of the study for each eligible patient will be immediately after signed written informed consent. The study will be considered complete after five patients have completed three post-Tc-99m MAA imaging assessments.
Study Duration	Enrollment is expected to be completed within 24 months; therefore, the total study duration is estimated to be 24 months.
Participant Duration	The study duration for each subject is expected to be up to 24 hours.
Inclusion Criteria	1. Patients 21 years and older 2. Patient written informed consent 3. Patients who receive Tc-99m MAA while being evaluated for TheraSphere treatment
Exclusion Criteria	1. Patients who are contraindicated for TheraSphere treatment 2. Patients who are contraindicated for Tc-99m MAA per the applicable Package Insert 3. Patients who do not receive Tc-99m MAA during pre-treatment Y-90 mapping

Patient Exposure Study	
Statistical Methods	
Statistical Test Method	No formal hypothesis testing is proposed for the study assessment. Analyses and summaries will be descriptive.

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

4.1. *Background and Study Rationale*

TheraSphere is a Y-90 glass microsphere therapy for Selective Internal Radiation Therapy (SIRT) in hepatocellular carcinoma (HCC). The treatment goal of SIRT is to selectively target and deliver a tumoricidal radiation dose to tumors within the liver, while maintaining an acceptable radiation dose to the normal liver tissue.

TheraSphere is administered through the hepatic artery which supplies blood to the hepatic tumors. The mean tissue penetration of the beta energy from the Y-90 in the microspheres is approximately 2.5 mm, with a maximum range up to 11 mm. Cancer cells adjacent to the embedded microspheres are killed while the nearby hepatic parenchyma and tissues in adjacent organs are generally spared the destructive effects of the beta radiation.

The United States Food and Drug Administration (FDA) approved the use of TheraSphere to treat unresectable HCC on March 17, 2021.

Prior to administration of TheraSphere, hepatic arteriography and Technetium-99m macroaggregated albumin (Tc-99m MAA) scanning are performed to detect extrahepatic shunting to the lung or the gastrointestinal tract.

This study is being conducted, at the request of the FDA, to provide data to calculate the radiation-absorbed dose of Tc-99m MAA to the whole body and to potential irradiated non-liver critical organs.

5. Study Product Description

Lung perfusion scintigraphy with Tc-99m MAA is an important diagnostic tool in SIRT planning. Tc-99m MAA is utilized as a TheraSphere surrogate.

There are several Tc-99m MAA imaging agents that have been approved by the FDA that can be used for TheraSphere pre-treatment mapping. The specific brand of Tc-99m MAA imaging agent that is used is at the discretion of the physician.

Several studies have examined the biodistribution of Tc-99m MAA as used in TheraSphere pre-treatment planning procedures. Bailey et al published a retrospective case series review of 70 HCC patients and examined extrahepatic uptake using combined planar and SPECT/CT imaging (1). Results showed the largest uptake was seen in the renal cortex, salivary glands, thyroid gland and gastric mucosa amongst 70 patients (100%), 23 patients (33%), 23 patients (33%) and 32 patients (46%), respectively. Lesser uptake was noted in other organs in fewer patients. This extrahepatic deposition is thought to be a result of deposition of Tc-99m MAA breakdown products such as free Tc-99m-pertechnetate which is released over time (1) (2) (3). In the gastric mucosa and thyroid gland, free ^{99m}Tc-pertechnetate deposition is visualized as a diffuse pattern and in the stomach is distinguishable from non-target Tc-99m MAA delivery and does not represent non-target administration or a pathologic concern (3) (4). Uliel et al suggested that using a high labelling efficiency Tc-99m-pertechnetate and minimizing the time interval between radiotracer injection and imaging time reduces the amount of nonspecific background activity (3).

In clinical practice, there is typically a delay between Tc-99m MAA injection and imaging during which dissociation of the Tc-99m MAA occurs. Grosser et al found that there was a time-dependent significant release of free 99mTc from the liver over a 24-hour time period after examining scans taken at 1, 5 and 24 hours after intraarterial Tc-99m MAA injection (5). The biexponential decay curve can be best described as: T half-life, fast = 7.9 hours, T half-life, slow =22.4 hours; adjusted R^2=0.77. The authors therefore recommended that liver perfusion scintigraphy with Tc-99m MAA be performed no later than four hours after injection. De Gersem et al did a similar study performing whole body scans at < 1 hour, between 1 and 4 hours, and > 4 hours post Tc-99m MAA injection (2). They found higher levels of radioactivity in the lung (extrahepatic deposition) in the > 4 hour scans than in the < 1 hour scans. This overestimation has clinical relevance as the authors conclude that based on > 4 hour scan results, several patients would have been excluded from receiving radioembolization. The longer imaging is delayed post radiotracer injection, the more free Tc-99m is released. The same logic can be applied to extrahepatic activity seen on imaging post Tc-99m MAA injection. Indeed, Bailey et al did not note any correlation between extrahepatic uptake and time to imaging however their mean interval was only 92 minutes (1).

In summary, several authors have described the reasons for extrahepatic organ uptake of Tc-99m MAA degradation products as visualized on imaging. Presence of radiotracer in these organs originates from Tc-99m MAA degradation products and does not pose a clinical concern (3). Keeping the time interval between radiotracer injection and imaging as short as possible limits the distribution of radiotracer degradation products to extrahepatic tissue (1).

6. Study Objective

The objective of this study is to provide data to calculate the radiation-absorbed dose of Tc-99m MAA to the whole body and to potential irradiated non-liver critical organs.

7. Study Design

The TheraSphere Post-Approval Study is a post-market, prospective, single-arm, open-label, observational study to support the use of TheraSphere for the treatment of hepatocellular carcinoma.

7.1. *Scale and Duration*

This study is planned to be conducted at up to 3 clinical study sites in the United States. Five patients will be enrolled in the study.

A patient is considered enrolled once an informed consent form has been signed, and all inclusion and no exclusion criteria have been met.

If the patient is found to not meet the inclusion criteria, the patient should not be included in the study.

Patients enrolled in the study will have 3 images taken after Tc-99m MAA injection. The final image will occur between 18 and 24 hours after Tc-99m MAA injection.

Enrollment is expected to be completed within 24 months; therefore, the total study duration is estimated to be 24 months.

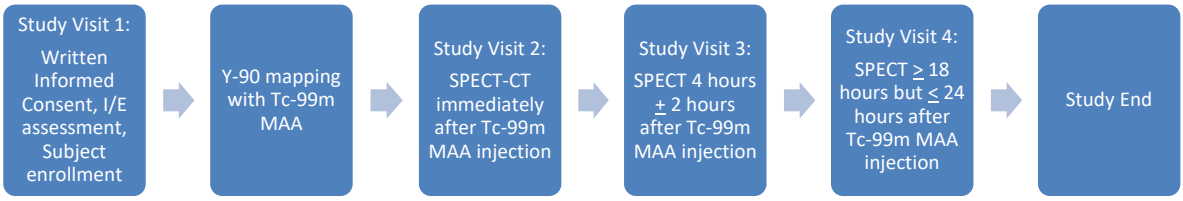


Figure 7.1-1: TheraSphere Post-Approval Study Design

7.2. *Justification for the Study Design*

This post-market study is being conducted at the direction of the FDA. Eligible study patients, after discussion and agreement with their treating physician, will be undergoing evaluation for the delivery of TheraSphere for the treatment of HCC. This study will provide data on the pre-Y-90 radiation-absorbed dose risk of Tc-99m MAA to the whole body and to potential irradiated non-liver critical organs.

8. Subject Selection

8.1. *Study Population and Eligibility*

The intended population for the TheraSphere Post-Approval study is patients with HCC who are undergoing evaluation to assess eligibility for TheraSphere treatment.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

Table 8.2-1: Inclusion Criteria

Inclusion Criteria	1. Patients 21 years and older 2. Written informed consent 3. Patients who receive Tc-99m MAA while being evaluated for TheraSphere treatment

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 8.3-1) will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

Exclusion Criteria	1. Patients who are contraindicated for TheraSphere treatment 2. Patients who are contraindicated for Tc-99m MAA per the applicable Package Insert 3. Patients who do not receive Tc-99m MAA during pre-treatment Y-90 mapping

9. Subject Accountability

9.1. *Point of Enrollment*

Patients who provided written informed consent, meet all inclusion criteria and meet no exclusion criteria are considered enrolled in the study.

9.2. *Withdrawal*

Patients may leave the study at any time for any reason and without any consequences. The Investigator or designee will try to obtain the reason for study withdrawal and document this in the source data. An Investigator may discontinue a patient from the study, with or without the patient's consent, for any reason that may, in the Investigator's opinion, negatively affect the well-being of the patient. If a patient is withdrawn from the study, the Investigator will promptly inform the patient and sponsor. Data already collected will be retained and reported; however, no new data will be collected after the withdrawal.

Patients withdrawn from the study for any reason will be asked to participate in a limited capacity by allowing their medical status to be followed by telephone contact, medical chart review, or other agreed upon method. If a patient decides not to continue participation in a limited capacity, the Investigator will not access their medical record or other confidential records for new purposes related to the study; however, study data collected prior to their withdrawal may be reviewed and publicly available records may be consulted prior to or after their withdrawal.

9.3. *End-of-Study Definition*

The study will be considered complete after five patients have three post-Tc-99m MAA imaging assessments.

10. Study Methods

10.1. *Data Collection*

The data collection schedule is shown in Table 10.1-1.

Table 10.1-1: Schedule of Assessments

Procedure/Assessment	Study Visit 1: Screening and Enrollment	Study Visit 2: Immediately following Tc-99m MAA injection	Follow-up Visits	
			Study Visit 3: 4 hours (± 2 hours) following Tc-99m MAA injection	Study Visit 4: ≥ 18 hours but ≤ 24 hours following Tc-99m MAA injection
Informed consent process, including informed consent signature date	X			
Inclusion/Exclusion Criteria Assessment	X			
Demographics	X			
Medical history	X			
SPECT-CT		X		
SPECT			X	X
Procedure-related Serious Adverse Events assessment		X	X	X

10.2. *Study Candidate Screening*

A patient is considered enrolled once an informed consent form has been signed, and all inclusion and no exclusion criteria have been met.

If the patient is found to not meet the inclusion criteria, the patient should not be included in the study, nor should the patient be followed post-procedure per protocol.

10.2.1. Strategies for Recruitment and Retention

The intended population for the this study are patients who are undergoing evaluation for the use of TheraSphere to treat HCC. Patients may be recruited through the Investigator's practice or referring physicians. Any information disseminated to potential patients (e.g. advertisements, pamphlets, posters) must be approved by the investigational center's IRB prior to use.

Every effort must be made by the site to collect patient data per the Data Collection Schedule in Section 10.1.

10.3. *Informed Consent*

Before any study-specific tests or procedures are performed, patients will be asked to read and sign the IRB-approved study Informed Consent Form (ICF). Patients must be given ample time to review the ICF and have questions answered before signing.

Refer to section 9.1 for definition of point of enrollment.

10.4. *Study Visit 1: Screening Visit*

After a patient has given written informed consent, the following data should be collected. Data may be collected within 30 days prior to the Tc-99m MAA injection.

- Inclusion/Exclusion criteria assessment
- Demographics
- Medical history

10.5. *Study Visit 2: Immediately following Tc-99m MAA Injection*

Immediately following the injection of Tc-99m MAA during Y-90 mapping, the following data should be collected:

- Procedural and study product data
- Tc-99m MAA SPECT-CT
- Procedure-related serious adverse events

NOTE: all adverse events related to Tc-99m MAA should be reported to the applicable manufacturer through their defined Post-Market Surveillance procedure.

10.6. *Study Visit 3: 4 hours (± 2 hours) following Tc-99m MAA Injection*

At 4 hours (±2 hours) following the injection of Tc-99m MAA during Y-90 mapping, the following data should be collected:

- Tc-99m MAA SPECT
- Procedure-related serious adverse events

NOTE: all adverse events related to Tc-99m MAA should be reported to the applicable manufacturer through their defined Post-Market Surveillance procedure.

10.7. *Study Visit 4: ≥ 18 hours but ≤ 24 hours following Tc-99m MAA Injection*

At least 18 hours, but no more than 24 hours, following the injection of Tc-99m MAA during Y-90 mapping, the following data should be collected:

- Tc-99m MAA SPECT
- Procedure-related serious adverse events

NOTE: all adverse events related to Tc-99m MAA should be reported to the applicable manufacturer through their defined Post-Market Surveillance procedure.

10.8. *Study Completion*

A patient's participation in the study will be complete after the final data point in Study Visit 4 has been collected. Serious procedure-related adverse events that are still ongoing at the end of the subject's participation in the trial will be followed up for resolution status and this information will be provided to BSC for the purpose of regulatory agency reporting for the trial.

10.9. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

11. Statistical Considerations

The details of all statistical analyses will be described in the Statistical Analysis Plan.

11.1. *Primary Endpoints*

The endpoints of the study are the mean absorbed doses and delivered activity for whole body and for critical organs (including whole body effective dose). The mean and standard deviation will be summarized for each of these.

11.2. *Sample Size*

A formal sample size was not conducted for this study; however, five patients with three images each are required.

11.3. *General Statistical Methods*

11.3.1. Analysis Sets

The Intent to Treat (ITT) population will comprise of all patients enrolled in the study that meet eligibility criteria. All analyses will be performed on the ITT population.

11.3.2. Control of Systematic Error/Bias

To minimize patient selection bias, all consecutively eligible patients, who provide written informed consent, will be included in the study.

11.4. *Data Analyses*

Analyses and summaries will be descriptive. For continuous and/or ordinal variables, the descriptive statistics will include number evaluated, mean, standard deviation, median, quartiles, minimum and maximum. Categorical data will be summarized with observed counts and percentages for each category.

11.4.1. Other Endpoints/Measurements

Demographics data and medical history will also be summarized. Additionally, SAEs related to the procedure will be summarized. SAEs will be coded according to MedDRA.

11.4.2. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason.

12. Data Management

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to "Read only" after all data is either "Hard Locked" or "Entry Locked". Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all of the closeout activities are completed a request to IT is submitted to have the "Database Locked" or Decommissioned and all database access revoked.

12.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB, and the regulatory authority if applicable of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days

after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

Protocol deviations related to informed consent, inclusion/exclusion criteria and safety reporting, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor within the EDC. Sites may also be required to report deviations to the IRB, and the regulatory authority, per local guidelines and national/government regulations.

Protocol deviations not related to the informed consent process, eligibility, or safety reporting are not required to be reported to the sponsor for this study. Every attempt should be made to perform procedures and collect data according to this protocol.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB/FDA notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

The sponsor will not approve protocol waivers.

14. Compliance

14.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator. This study will be conducted in accordance with 21 CFR 50 and 56, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/ or regulatory authority shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date

curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation related to informed consent, inclusion/exclusion criteria, and safety reporting from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the procedure) every adverse event as applicable per the protocol.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the IRB and regulatory authorities any adverse events as required by applicable laws or regulations or this protocol or by the IRB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together

with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).

- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

14.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3. *Institutional Review Board*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB and ICF, must be received by the sponsor before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the ICF will be IRB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB requirements. Copies of the study reports and the IRB continuance of approval must be provided to the sponsor.

14.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

14.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

15. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

16. Potential Risks and Benefits

16.1. *Package Insert*

Please refer to the applicable Manufacturer’s Package Insert for the Tc-99m MAA for an overview of anticipated adverse events and risks associated to the product.

16.2. *Risks associated with Participation in the Clinical Study*

As this study is a post-market observational study, the additional risk associated with participating in this study is related to the collection of patient data and confidentiality thereof.

There may be additional risks linked to the procedure, and follow-up testing which are unforeseen at this time.

16.3. *Possible Interactions with Concomitant Medical Treatments, if applicable*

Refer to the Tc-99m MAA-specific Package Insert for recommendations and for further information on interactions and side effects associated with concomitant medical treatments following the procedure.

16.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.5. *Anticipated Benefits*

Patients may or may not receive benefits from participating in this study. Medical science and future patients may benefit from the results of this study.

17. Safety Reporting

17.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of the following categories:

- All procedure related serious adverse events
- New findings/updates in relation to already reported events
- All adverse events related to Tc-99m MAA should be reported to the applicable manufacturer through their defined Post-Market Surveillance procedure.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the Tc-99m MAA or procedure, it should be submitted to BSC as a procedure-related adverse event.

Any reportable event, experienced by the study subject after informed consent, whether prior to, during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an SAE, but should only be reflected as an outcome of one (1) specific SAE (see Table 17.2-1 for AE definitions).

Refer to the applicable Package Insert for the known risks associated with Tc-99m MAA.

17.2. *Definitions and Classification*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the safety definitions from ISO 14155 and EU 2017/745 for clarification purposes.

Table 17.2-1: Safety Definitions

Term	Definition
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)

Table 17.2-1: Safety Definitions

Term	Definition
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

17.3. *Relationship to Procedure*

The Investigator must assess the relationship of the reportable SAE to the study procedure. See criteria in Table 17.3-1:

NOTE: Only procedure-related serious adverse events are required to be reported to BSC through the EDC. To avoid administrative errors, the table below has been left in its entirety.

Table 17.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device, comparator or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 17.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device or comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 17.4-1.

Table 17.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 calendar days after becoming aware of the event or as per local/regional regulations. • Reporting required through end of study.

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor

17.5. *Reporting to Regulatory Authorities / IRBs / Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRBs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB, and regulatory authorities of SAEs as required by local/regional regulations.

18. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to any study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g., CRO), and approved by the site's IRB, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,

- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

19. Committees

19.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation group review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Medical Safety and Safety Trial Operations team include health care providers with expertise in oncology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

20. Suspension or Termination

20.1. *Premature Termination of the Study*

Boston Scientific, in collaboration with the FDA, reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific reasons and reasons related to protection of subjects. Investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

20.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following:

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

20.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB Approval*

Any investigator, or associated IRB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB terminates participation in the study, participating investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility, detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents, unless this action would jeopardize the rights, safety, or welfare of the subjects.

20.4. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond one year after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

The IRB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

21. Study Registration and Results

21.1. *Study Registration*

If required, to comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

21.2. *Clinical Investigation Report*

Progress reports will be submitted to FDA every six months until enrollment is complete and annually thereafter until the study is complete. Complete study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

21.3. *Publication Policy*

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.

- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

22. Bibliography

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23. Abbreviations and Definitions

23.1. *Abbreviations*

Abbreviations are shown in Table 23.1-1.

Table 23.1-1: Abbreviations

Abbreviations	Term
AE	Adverse Event
Bq	Becquerel
BSC	Boston Scientific Corporation

Abbreviations	Term
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
Gy	Gray
HCC	Hepatocellular Carcinoma
ICF	Informed Consent Form
IRB	Institutional Review Board
SAE	Serious Adverse Event
SIRT	Selective internal radiation therapy
SPECT	Single Photon Emission Computed Tomography
SPECT-CT	Single Photon Emission Computed Tomography in conjunction with Computed Tomography
Tc-99m MAA	Technetium-99m macroaggregated albumin
Y-90	yttrium-90

23.2. *Definitions*

Terms are defined in **Table 23.2-1**.

Table 23.2-1: Definitions

Term	Definition
Complication	An undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to perforation, occlusion, vessel spasm, etc. Complications may or may not be related to the procedure or commercial product.
Source data *Ref: ISO 14155*	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation Note 1 to entry: This includes source data initially recorded in an electronic format.
Source document *Ref: ISO 14155*	Original or certified copy of printed, optical or electronic document conaining source data.

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