Boston Scientific

NCT05233098

Document Date: January 4, 2023

# Statistical Analysis Plan

## TheraSphere Post-Approval Study

**Study Reference number: S2494**

**CONFIDENTIAL**

**DO NOT COPY OR DISTRIBUTE WITHOUT WRITTEN PERMISSION**

**APPROVALS (Check/Complete one below):**

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

| | |
|---|---|
| Lead Biostatistician – Lei Zhang, Fellow Biostatistics | Date (dd-mon-yyyy) |
| Clinical Project/Trial Manager – Michelle Wells, Sr. Manager, Clinical Research | Date (dd-mon-yyyy) |
| Medical Director – Eveline Boucher, Director, Medical Safety | Date (dd-mon-yyyy) |

# TABLE OF CONTENTS

# 1 REVISION HISTORY

| Document Revision Number | Template Number and Version | Section | Change | Reason for Change |
|---|---|---|---|---|
| A | 90702621 Rev/Ver AF | | Initial Document | Initial Release |
| B | 90702621 Rev/Ver AF | Section 2, 3, 4 and 5.3<br>Listing 16.2.1.2 | • Remove IFU requirement<br>• Remove abbreviations that are not applicable<br>• Change the number of study sites from one to up to three | • Updates to reflect the change in eligibility criteria in protocol to support study enrollment<br>• Keep consistency with protocol |

# 2 ABBREVIATION

| Abbreviation | Description |
|---|---|
| BMI | Body Mass Index |
| eCRF | Electronic Case Report Form |
| FDA | The United States Food and Drug Administration |
| HCC | Hepatocellular Carcinoma |
| ICF | Informed Consent Form |
| ITT | Intention-To-Treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PAS | Post-Approval Study |
| PP | Per-Protocol |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SIRT | Selective Internal Radiation Therapy |
| SOC | System Organ Class |
| Tc-99m MAA | Technetium-99m Macroaggregated Albumin |

# 3 PROTOCOL SUMMARY

TheraSphere is a Y-90 glass microsphere therapy for Selective Internal Radiation Therapy (SIRT) in hepatocellular carcinoma (HCC). Its treatment goal 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. 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. At the request of the FDA, the TheraSphere Post-Approval Study (PAS) is being conducted to evaluate the pre-Y-90 radiation-absorbed dose risk of Tc-99m MAA to the whole body and to potential irradiated non-liver critical organs.

TheraSphere PAS is a post-market prospective, single-arm, open-label, observational study. Its primary objective is to calculate the radiation-absorbed dose of Tc-99m MAA to the whole body and to non-liver critical organs. The study will be conducted at up to three clinical study sites in the US, and plans to enroll a total of five patients who are being evaluated for TheraSphere administration.

Study subjects will be required to provide written informed consent prior to any study procedures being conducted. Those who provide written informed consent, fulfill all the inclusion criteria and meet none of the exclusion criteria will be considered enrolled in the study. Subjects enrolled in the study will have 3 images taken after Tc-99m MAA injection: immediately after the injection, 4 hours (within ±2 hours window) after the injection, and between 18 and 24 hours after Tc-99m MAA injection (Figure 1.1).

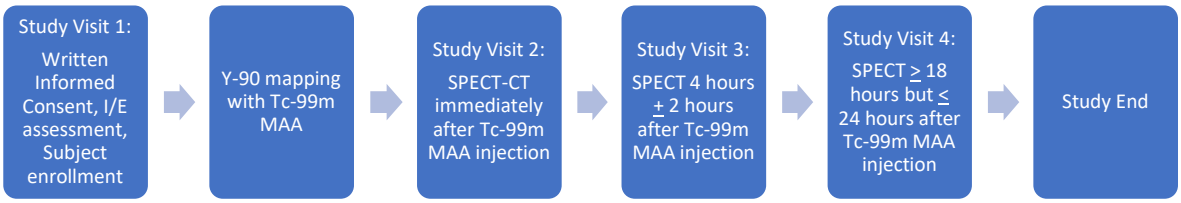


**Figure 1:** TheraSphere Post-Approval Study Design

## 4 INTRODUCTION

The statistical analysis plan (SAP) is based on protocol version B dated 27Oct2022 and the electronic case report form (eCRF) version 4.0 dated 05Dec2022. It will further describe the analysis outlined in the protocol. A mock-up of tables, listings and figures (TLFs) will be provided in this document.

## 5 GENERAL STATISTICAL METHODS

Continuous data will be summarized with mean, median, standard deviation, quartiles (25th and 75th), minimum and maximum, unless otherwise specified. Categorical data will be summarized with observed counts and percentages for each category. The number and percentage of subjects with missing data will also be provided.

### 5.1 Analysis Sets

The Intention-To-Treat (ITT) population will comprise of all subjects enrolled in the study that meet eligibility criteria. All analyses will be performed on the ITT population.

The Per-Protocol (PP) population will include all ITT population without any major protocol deviation that could impact the primary endpoint analysis, such as missing SPECT-CT/SPECT scans.

### 5.2 Control of Systematic Error/Bias

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

### 5.3 Number of Subjects per Investigative Site

The study will be conducted at up to three clinical study sites in the US and plans to enroll a total of five subjects.

## 6 ENDPOINT ANALYSIS

### 6.1 Primary Endpoint

The endpoints of the study are the mean absorbed doses and delivered activity for whole body and for non-liver critical organs (including whole body effective dose). Non-liver critical organs include lungs, salivary gland, thyroid gland, stomach mucosa/wall, gallbladder wall, small intestine mucosa/wall, colon mucosa/wall, urinary bladder wall, kidneys, spleen, and heart wall.

Tc-99m MAA activity is measured through SPECT-CT/SPECT scans immediately after the injection, 4 hours (within ±2 hours window) after the injection, and between 18 and 24 hours after the injection. For each organ, a plot of activity and time from Tc-99m MAA administration will be constructed, and an appropriate graphing software will be used to fit a curve to the data. The cumulative activity (area under the curve) divided by the administered activity will be used as an input to S-value-based dosimetry software to determine absorbed dose and effective absorbed dose.

Descriptive statistics will be used to summarize delivered activity for whole body and for non-liver critical organs at post-Tc-99m MAA injection, 4 hours after the injection and 18-24 hours after the injection. Descriptive statistics will be also used to summarize the mean absorbed dose and effective dose for whole body and for non-liver critical organs.

### 6.2 Sample Size

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

## 7 ADDITIONAL DATA ANALYSES

### 7.1 Other Endpoints/Measurements

Subject disposition, demographics and physical assessments will be summarized and listed. SAEs related to the procedure will be listed. SAEs will be coded according to MedDRA. In addition, Tc-99m MAA administration, and its deposition in critical organs assessed by SPECT-CT/SPECT will also be listed.

**Disposition**

- Number of subjects screened

- Number and percentage of subjects in ITT population and PP population
- Number of subjects completing the study
- End of study reason
  - Investigator withdrawal
  - Subject withdrawal
  - Death
  - Other

**Demographic**

- Age at consent (years)
- Gender (Male, Female, Other),
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown, Other)
- Ethnicity (Hispanic, Latinx, or of Spanish origin, Not Hispanic, Latinx or of Spanish origin, Not reported, Unknown)

**Physical Assessments**

- Height (m)
- Weight (kg)
- BMI ($kg/m^2$) (calculated as weight in kg divided by square of height in m)

**HCC History**

- Time since diagnosis (months). It is calculated as the days between HCC diagnosis for current treatment and the administration of Tc-99m MAA divided by 30.4375.

### 7.2 Protocol Deviations

The inclusion and exclusion criteria were developed to minimize the number of protocol deviations in this study. Any protocol deviations that are captured will be listed.

## 8 CHANGES TO PLANNED ANALYSES

Any changes to the planned statistical analyses made prior to performing the primary analyses will be documented in an amended SAP 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 for the deviation.

## 9 VALIDATION

All clinical data reports generated per this plan will be validated through the internal validation process used by the independent CRO. BSC Global WI 90702587: Clinical Data Reporting Validation may be used as a guidance. Statistical analyses and validation will be done by the independent CRO.

## 10 PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by the independent CRO. All programming considerations are aimed at facilitating the programming codes generation (e.g. SAS codes).

In general, data listings should be sorted by subject ID and visit/collection dates.
In adverse events, the sorting sequence should be subject ID and the start date of the event. Other sorting sequence that differs from these will be specified. Table and listing display should follow the guidelines listed below:

- All data in the listings should represent the original values that were recorded in the eCRFs, unless otherwise specified.
- Missing values should be printed as blanks in the listings.
- Dates should be printed in Date9 format (DDMMMYYYY).
- In general, for categorical variable summary, if there is missing data, an additional category of 'Missing' should be created, and the number and percentage should be provided.
- In general,
    - the mean (standard deviation) of a set of values should be printed out to one (two) more decimals than the raw value.
    - the median and percentiles should be printed out to one more decimals than the raw value.
    - the minimum and maximum should be printed out to the same number of decimals as the raw value
    - All percentages should be reported with one decimal point.
- All tables and figures will have a footnote indicating corresponding reference listing(s), such as "Reference Listing: xx.x". Additionally, tables and figures will have a footnote indicating the corresponding reference table(s), if applicable.
- Footers should include data source, date of data extract/snapshot and SAS program name. If an additional cut-off date is being used; this should also be included. This should come after all relevant footnotes in the output.
- Tables will ensure page breaks don't occur in the middle of statistical table blocks, unless unavoidable
- For listings with multiple records for subjects, repeat values of the subjects will be greyed out
- If a planned table does not have any data to summarize, it will still be created with the statement "No subjects qualify for this table." This will also be applied to listings and figures.

## 11 TABLES AND LISTINGS SHELLS

This section will give the format and structure of all tables and listings to be produced. These detailed specifications can undergo minor revisions during the production phase without needing to revise the SAP. Minor revisions are defined as revisions that do not invalidate any of the specifications in this SAP.

**Table 14.1.1 Subject Disposition – All Subjects**

| | Subjects |
|---|---|
| **Patients Screened** | xx |
| **Populations, n (%)** | |
| ITT[a] | xx (xx.x) |
| PP[b] | xx (xx.x) |
| **Study Status, n (%)[c]** | |
| Subject completed the study | xx (xx.x) |
| Investigator withdrawal | xx (xx.x) |
| Subject withdrawal | xx (xx.x) |
| Subject died | xx (xx.x) |
| Other | xx (xx.x) |

[a] ITT is defined as subjects who were enrolled and meet the eligibility criteria.
[b] PP is defined as ITT subjects without any major protocol deviation, such as missing SPECT-CT/SPECT scans.
[c] Percentages are based on the number of subjects in the ITT population

**Table 14.2.1 Primary Endpoint Summary – ITT Population**

| | ITT Population (N=XX) |
|---|---|
| **Delivered Activity for Whole Body (MBq)** | |
| **Immediately following** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |
| **4 hours +/- 2 hours** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |
| **18-24 hours** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |
| **Delivered Activity for Non-Liver Critical Organs (MBq)** | |
| **Immediately following** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |
| **4 hours +/- 2 hours** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |
| **18-24 hours** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |
| **Absorbed Dose (Gy) – Whole Body** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |

| | ITT Population (N=XX) |
|---|---|
| **Absorbed Dose (Gy) – Non-Liver Critical Organs** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |
| **Effective Dose (mSv) – Whole body** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |
| **Effective Dose (mSv) – Non-Liver Critical Organs** | |
| n | xx |
| Mean (SD) | xx (xx.x) |
| Median | xx |
| Q1, Q3 | xx, xx |
| Min, Max | xx, xx |

*Programming note: delivered activity for non-liver critical organs is the sum of all the individual activity for non-liver critical organs including others. The same thing is applied to absorbed dose and effective dose.*

## Listing 16.2.1.1 Disposition – All Subjects

| Subject ID | ITT Population | PP Population | Consent Date | Version of ICF | End of Study Date | End of Study Reason |
|---|---|---|---|---|---|---|
| xxxxxxxx | Yes | Yes | ddMMMyyyy | xx.xx | ddMMMyyyy | xxxxx |
| xxxxxxxx | No | No | | | | Other: *specify* |

## Listing 16.2.1.2 Inclusion/Exclusion – All Subjects

| Site # | Subject ID | Meet Eligibility? | Inclusion Criteria Not Met | Exclusion Criteria Met |
|---|---|---|---|---|
| xx | xxxxxxxx | Yes | | |
| xx | xxxxxxxx | No | Inclusion 1: Patients 21 years and older;<br>Inclusion 3: Patients who receive Tc-99m MAA while being evaluated for TheraSphere treatment | Exclusion 2: Patients who are contraindicated for Tc-99m MAA per the applicable Package Insert |

## Listing 16.2.1.3 Demographics – ITT population

| Subject ID | Age at Consent (years) | Gender at birth | Race | Ethnicity | Height (unit) | Weight (unit) | BMI ($kg/m^2$)[a] | HCC Diagnosis Date for Current Treatment | Months since Diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| xxxxxxxxxx | xx | xx | xx | xx | xx (cm) | xx (kg) | xx | ddMMMyyyy | xx.x |
| xxxxxxxxxx | xx | xx | xx | xx | xx (in) | xx (lb) | xx | ddMMMyyyy | xx.x |

[a]BMI is calculated as weight (kg)/height $(m)^2$

## Listing 16.2.1.4 Protocol Deviations – ITT population

| Subject ID | Date of Deviation | Folder /Form | Category | Reason |
|---|---|---|---|---|
| xxxxxxx | ddMMMyyyy | | Other: *specify* | |
| xxxxxxx | ddMMMyyyy | | Event not reported per protocol: AE number | |

## Listing 16.2.2.1 Tc-99m MAA Administration – ITT population

| Subject ID | Date of Administration | Time of Administration | Vascular Access | Tc-99m MAA activity in syringe before injection (unit) | Tc-99m MAA injection volume (cc) | Tc-99m MAA activity remaining in syringe (unit) | Location of Tc-99m MAA injection |
|---|---|---|---|---|---|---|---|
| xxxxxxx | ddMMMyyyy | xx:xx | Femoral Artery | xx (mBq) | xx | xx (mBq) | *List all the locations* |
| xxxxxxx | ddMMMyyyy | xx:xx | Radial Artery | xx (mBq) | xx | NA | |
| xxxxxxx | ddMMMyyyy | xx:xx | Femoral Artery | xx (mCi) | xx | xx (mCi) | |

## Listing 16.2.2.2 Imaging Information – ITT population

| Subject ID | Time from Tc-99m MAA Administration | Image Modality | Date of Image | Time of Image |
|---|---|---|---|---|
| xxxxxxxx | Immediately following | SPECT-CT | ddMMMyyyy | xx:xx |
| | 4 hours +/-2 hours | SPECT | ddMMMyyyy | xx:xx |
| | 18-24 hours | SPECT | ddMMMyyyy | xx:xx |
| xxxxxxxx | Immediately following | SPECT-CT | ddMMMyyyy | xx:xx |
| | 4 hours +/-2 hours | SPECT | ddMMMyyyy | xx:xx |
| | 18-24 hours | SPECT | ddMMMyyyy | xx:xx |

## Listing 16.2.2.3 Tc-99m MAA Deposition – ITT population

| Subject ID | Region | Volume (cc) | Activity (MBq) | | | Absorbed Dose (Gy) | Effective Dose (mSv) |
|---|---|---|---|---|---|---|---|
| | | | Immediately following | 4 hours +/-2 hours | 18-24 hours | | |
| xxxxxxxx | Liver | xx | xx | xx | xx | xx | xx |
| | Lungs | xx | xx | xx | xx | xx | xx |
| | Salivary gland | xx | xx | xx | xx | xx | xx |
| | Thyroid gland | xx | xx | xx | xx | xx | xx |
| | Stomach mucosa/wall | xx | xx | xx | xx | xx | xx |
| | Gallbladder wall | xx | xx | xx | xx | xx | xx |
| | Small intestine mucosa/wall | xx | xx | xx | xx | xx | xx |
| | Colon mucosa/wall | xx | xx | xx | xx | xx | xx |
| | Urinary bladder wall | xx | xx | xx | xx | xx | xx |
| | Kidneys | xx | xx | xx | xx | xx | xx |
| | Spleen | xx | xx | xx | xx | xx | xx |
| | Heart wall | xx | xx | xx | xx | xx | xx |
| | Other 1 | xx | xx | xx | xx | xx | xx |
| | Other 2 | xx | xx | xx | xx | xx | xx |
| | Other 3 | xx | xx | xx | xx | xx | xx |
| | Whole body | NA | xx | xx | xx | xx | xx |
| xxxxxxxx | Liver | xx | xx | xx | xx | xx | xx |
| | Lungs | xx | xx | xx | xx | xx | xx |
| | ……. | | | | | | |
| | Other 3 | xx | xx | xx | xx | xx | xx |
| | Whole body | NA | xx | xx | xx | xx | xx |

*Programming note: For others, please population the actual region in specify field.*

## Listing 16.2.3.1 Procedure-Related Serious Adverse Events – ITT population

| Subject ID | MedDRA SOC/ Preferred Term/ Verbatim Term | Onset Date | Awareness Date | Serious Criteria | Severity | Action Taken | Outcome |
|---|---|---|---|---|---|---|---|
| **xxxxxxx** | System Organ Class/ Preferred Term/ VERBATIM TERM* | ddMMMyyyy | ddMMMyyyy | xx | xx | Other: *specify*<br><br>Surgery: *specify*<br>Interventional procedure: *specify* | Resolved: Resolution date<br>Death: Death date |

*Programming note: For outcome, if it is Resolved or Death, please concatenate with date.*

# Boston Scientific
# Project Document Signature Page

Report Generated: 29-Jul-2024 16:59:44 (GMT)

**Criteria-** Full Lifecycle (All Votes)

**Object Number:** 92813549
**Name:** TheraSphere Statistical Analysis Plan
**Effective Date:** 04-Jan-2023 06:21 GMT
**CN Number:** 2573811

**State:** Released
**Revision:** B
**Sub Type:** null

## Signatures:

| Object Type | Number | Reviewer | Role | Vote | Vote Comments | Vote Date |
|---|---|---|---|---|---|---|
| Change Notice | 2573811 | Wells, Michelle | Clinical Project Management - Functional Representative | Approve | | 04-Jan-2023 15:50 GMT |
| Change Notice | 2573811 | Boucher, Eveline | Medical - Functional Representative | Approve | | 04-Jan-2023 17:55 GMT |
| Change Notice | 2573811 | Zhang, Lei | Biostatistics - Functional Representative | Approve | | 04-Jan-2023 18:21 GMT |