

# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Microspheres Radionuclide

Device Trade Name: TheraSphere™

Device Procode: NAW

Applicant's Name and Address: Boston Scientific Corporation  
11 Hines Road, Suite 200,  
Ottawa, Ontario K2K 2X1 Canada

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200029

Date of FDA Notice of Approval: March 17, 2021

## II. INDICATIONS FOR USE

TheraSphere is indicated for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable hepatocellular carcinoma (HCC), Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status.

## III. CONTRAINDICATIONS

TheraSphere is contraindicated in patients:

- whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques
- who show shunting of blood to the lungs that could result in delivery of greater than 16.5 mCi (0.61 GBq) of Y-90 to the lungs. Radiation pneumonitis has been seen rarely in patients receiving doses to the lungs greater than 30 Gy in a single treatment.
- in whom hepatic artery catheterization is contraindicated, such as patients with vascular abnormalities or bleeding diathesis
- who have pulmonary insufficiency (conventionally defined by an arterial oxygen pressure (Pa,O<sub>2</sub>) of < 60 mmHg, or oxygen saturation (Sa,O<sub>2</sub>) of < 90% (1)) or severe liver dysfunction, including hepatic encephalopathy, clinically evident ascites. or treatment with diuretics for ascites
- with portal vein thrombosis (PVT) Type 4 involvement and lack of Tc-99m MAA deposition on the PVT seen on the Tc-99m MAA imaging
- with >70% tumor replacement in the liver

- with comorbidities or poor overall health (e.g., Eastern Cooperative Oncology Group (ECOG) performance status rating >2) which may make the patient a poor candidate for locoregional radiation treatment
- who are pregnant

There are no data from the LEGACY study supporting the safety of TheraSphere use in patients with the contraindicated conditions.

#### IV. **WARNINGS AND PRECAUTIONS**

##### **WARNINGS**

The following pre-treatment, high-risk factors (disease characteristics) have been associated with serious adverse events deemed possibly related to use of the device:

- infiltrative tumor type
- tumor nodules too numerous to count
- AST or ALT > 5 times upper limit of normal (ULN)
- bilirubin > 2 mg/dL
- tumor volume > 50% combined with albumin < 3 g/dL

The TheraSphere dose vial must be kept upright and stored in its lead pot before and during patient treatment, except as required for radiation measurement. Do not open the dose vial acrylic shield prior to patient treatment. Post-treatment, waste materials require caution to prevent contamination and beta shielding due to residual glass microspheres.

##### **PRECAUTIONS**

###### **GENERAL PRECAUTIONS**

- As in any intra-arterial procedure, aseptic technique should be practiced, and care should be taken to ensure minimum patient anesthesia exposure extraneous to therapeutic objective.
- Consideration of patient comorbidities should be used when determining the type and volume of fluid to infuse via catheter to avoid electrolyte imbalance, fluid shift, and hyperglycemia.
- It is important to avoid any aggressive arterial procedure that may lead to arterial spasm that impairs TheraSphere distribution into the perfused liver target volume which may lead to underdosing or non-target deposition of TheraSphere.

###### **PRECAUTION IN PATIENTS WITH IMPAIRED LIVER FUNCTION**

- No effectiveness or safety data from the LEGACY study are available to support the use of the device in patients with Child-Pugh score B or C cirrhosis.

###### **PRECAUTION IN VULNERABLE PATIENTS**

- No effectiveness or safety data are available to support the use of the device in children or breast-feeding women.

## ENDOCRINE DISRUPTION, CARCINOGENICITY, MUTAGENICITY, TOXICITY TO REPRODUCTION

- Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

## RADIATION SAFETY

- Consult and follow all applicable regulatory agency requirements for safe handling and storage of radioactive materials. TheraSphere glass microspheres contain Y-90, a high-energy beta emitter.
- Radioactive products should be used only by healthcare professionals who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.
- As in the use of any radioactive material, ensure minimum radiation exposure to the patient extraneous to the therapeutic objective, and to minimize radiation exposure to workers and others in contact with the patient.
- The TheraSphere dose vial is supplied in an acrylic shield to fully attenuate beta particles and within a lead pot to further limit radiation exposure to secondary bremsstrahlung (x-ray) radiation. The TheraSphere dose vial should always be stored in a shielded location away from personnel.
- Always wear disposable gloves when handling the dose vial. Routinely check for radioactive contamination after handling.
- After the treatment, any spills or leaks must be cleaned up immediately. The treatment area and all personnel handling radioactive materials should be monitored for contamination.
- Radioactive waste must be contained and stored for waste disposal according to hospital procedures for radioactive materials.

## RELEASE AND POST-TREATMENT PRECAUTIONS

- Post treatment patient care: use universal precautions for body fluid contact. Trace Y-90 may be detectible in blood and urine; handle with gloves and dispose as normal body fluids. The radiation field is expected to be less than 1 mrem/h (10  $\mu$ Sv/h) at 3 ft (1 m) from the patient's abdomen. Supplemental shielding and segregation of the patient are not required to maintain exposure to others below regulated limits.
- Release instructions: The patient should follow good hygiene (e.g., proper hand washing). Caregivers, family, and others do not require restrictions on patient contact; however, they can minimize their radiation exposure by avoiding prolonged time (>12 hours per day) within 1 ft (0.3 m) of the patient's abdomen for the first week post therapy. Patients should be advised that radiation emitted from the patient may be detectible at security screening (e.g., international travel).
- Special precautions post-administration: If the patient requires hospitalization, surgery, medical assessment or treatment regarding any part of their thorax or abdomen within first 2 weeks of treatment, the patient should advise the hospital and treating physician of the Y-90 TheraSphere implant. The physician should consult their radiation safety staff for handling and disposal of liver tissue.
- Special liver tissue handling: Special liver tissue handling may be required for post-treatment surgery, explant, or transplant since the glass microspheres remain permanently

implanted in the liver tissue. Disclosure of the treatment will be required if cremation is considered.

#### TRAINING

- Administration of radioactive Y-90 microspheres requires expertise in hepatic vascular anatomy as well as angiographic, nuclear medicine, and radiographic procedures. Due to the technical expertise required for these various complex procedures, a multi-disciplinary approach including Radiology, Nuclear Medicine, Radiation Oncology, Medical Oncology, and Interventional Radiology is recommended. The institution must have the appropriate facilities, equipment, licenses and approvals to administer TheraSphere according to local regulations and authorities.
- All users must be appropriately trained and be experienced with the administration of Y-90 microspheres prior to the unsupervised use of TheraSphere. New site training is provided by the manufacturer of the device. All personnel participating in the use of the device must be trained, all required safety precautions must be taken, and all approvals must be in place prior to using TheraSphere for the first time. The site is responsible for all ongoing licensing and any additional training that may be needed.

## V. DEVICE DESCRIPTION

The TheraSphere Yttrium-90 Glass Microsphere System (TheraSphere) is comprised of the following components required for administration:

- TheraSphere Y-90 Glass Microspheres dose vial;
- TheraSphere Administration Set; and
- TheraSphere Administration Accessory Kit.

### A. TheraSphere Y-90 Glass Microspheres

TheraSphere Y-90 Glass Microspheres consist of insoluble glass microspheres, with sphere diameter of 15 to 35  $\mu\text{m}$ , where Yttrium-90 (Y-90) is an integral constituent of the glass. Y-90 is a pure beta emitter and decays to stable Zirconium-90 (Zr-90) with a physical half-life of 64.1 hours (2.67 days). Y-90 is used because it produces high-energy radiation with average energy emissions of 0.9367 MeV and relatively short tissue penetration (mean 2.5 mm, maximum 11 mm). Table 1 describes the Y-90 radioactive properties. The Y-90 glass microspheres are delivered into the liver tumor through a microcatheter placed into the hepatic artery branch that supplies blood to the tumor. The Y-90 glass microspheres are unable to pass through the vasculature of the liver due to arteriolar capillary blockade and are trapped in the tumor vasculature. The beta radiation emitted by Y-90 exerts a local radiotherapeutic effect to the tumor with some concurrent Y-90 radiation to surrounding normal liver tissue within the perfused liver volume. The radiation emitted by the glass microspheres diminishes substantially over the first 2 weeks after treatment. The glass microspheres remain permanently implanted in the liver tissue.

The TheraSphere Y-90 Glass Microspheres (dose vials) are supplied sterile and are available in 0.5 GBq increments between 3 GBq - 20 GBq (13.5 mCi increments between

81 mCi - 540 mCi). All dose sizes have a manufacturing tolerance of  $\pm 10\%$  of nominal activity. Each milligram of glass microspheres contains between 22,000 and 73,000 microspheres. They are supplied in 0.6 mL pyrogen-free water in a V-bottom vial enclosed in an acrylic shield and have a shelf-life of 12 days post calibration.

**Table 1: Yttrium-90 Radioactive Properties**

<b>Decay Product</b>	Zirconium-90
<b>Half-Life, <math>t_{1/2}</math></b>	64.1 hours (2.67 days)
<b>Average range of beta radiation in tissue</b>	0.1 in (2.5 mm)
<b>Initial radiation dose for 27 mCi (1 GBq) of Y-90 administered to 2.2 lb (1 kg) of liver tissue</b>	13 Gy / day (1,297 rad / day)
<b>Mean Life, <math>t</math></b>	3.85 days
<b>Radiation dose delivered to 2.2 lb (1 kg) of tissue from complete radioactive decay of 1 GBq (27 mCi) of Y-90</b>	13 Gy x 3.85 days = 50 Gy (5,000 rad)

### B. TheraSphere Administration Set

A preassembled, sterile, single-use TheraSphere Administration Set (Figure 1) is required for each dose vial and connects the dose vial containing the microspheres to the microcatheter (not provided) to enable delivery of the Y-90 glass microspheres from the dose vial into the hepatic artery. The TheraSphere Administration Set is intended to be used only in conjunction with the TheraSphere product.

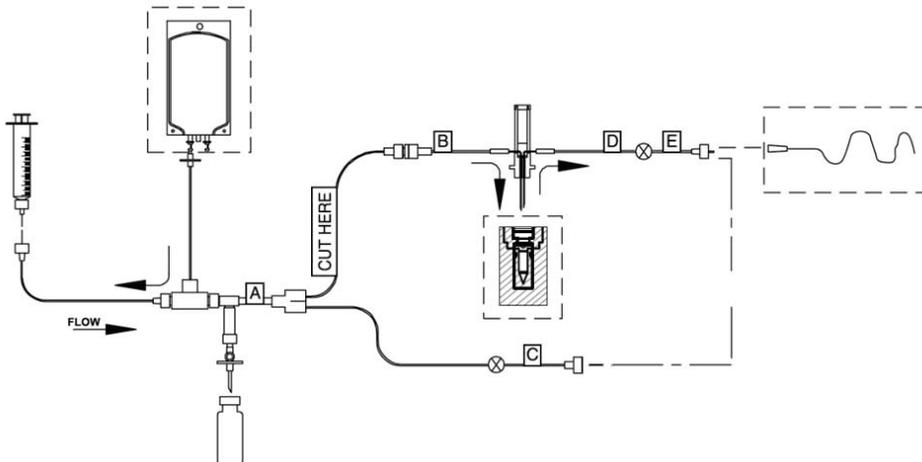


Figure 1. TheraSphere Administration Set Configuration (Items in dashed boxes are not supplied with the Administration Set)

### C. TheraSphere Administration Accessory Kit

The non-sterile, re-usable TheraSphere Administration Accessory Kit (Figure 2) ensures optimal layout of the TheraSphere Administration Set and the dose vial, facilitates monitoring of the infusion process, and provides beta radiation shielding. It is supplied to new user sites prior to their first TheraSphere administration.

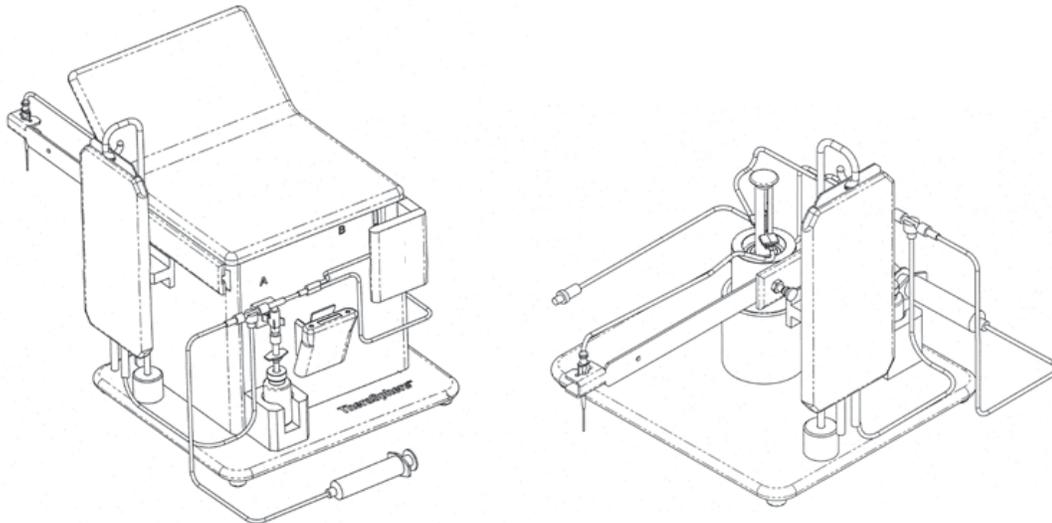


Figure 2. TheraSphere Administration Accessory Kit (Shown assembled with TheraSphere Administration Set)

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of unresectable hepatocellular carcinoma (HCC). Alternative treatment choice is largely dependent on the disease stage, treatment intent, and the patient's overall well-being. These can be divided into curative and palliative treatments. Alternative curative treatments for HCC include ablation, surgical resection, and transplantation. Alternative palliative treatments include transarterial chemoembolization (TACE), transarterial embolization (TAE), external radiation therapy, selective internal radiation therapy and systemic therapies such as immunotherapy, targeted biologic therapy or chemotherapy. Each alternative method for management of HCC has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## VII. MARKETING HISTORY

TheraSphere has been marketed commercially in the United States under HDE H980006 since the year 2000. TheraSphere has also been marketed in Canada since 2005, in several European Union countries as early as 2006, and in the Middle East, Asia, and Latin America since 2009, 2015 and 2018, respectively. TheraSphere has not been withdrawn from commercial distribution (marketing) in any country for any reason related to safety and effectiveness.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. The use of this product leads to irradiation of both tumorous and normal liver tissue; as a result, patients with compromised liver function may be at greater risk of liver function impairment, hence could experience complications. See “**WARNINGS**” for more information. Any serious incident that occurs in relation to this device should be reported to the manufacturer and relevant local regulatory authority.

Clinical side effects usually occur within the first 4 to 6 weeks after treatment.

Based on clinical trial data, literature reviews and post market surveillance, adverse events potentially associated with treatment using Y-90 microspheres, including TheraSphere, may include the following:

- Allergic reaction
- Altered liver function, acute or chronic
- Anorexia
- Anxiety
- Ascites
- Bile Duct injury
- Bleeding/hemorrhage
- Chills / rigors
- Cholecystitis (inflammatory or infectious)
- Colitis
- Death
- Dehydration
- Diarrhea
- Dizziness
- Dyspnea
- Edema (any location)
- Electrolyte abnormalities
- Elevated BUN/creatinine
- Fall
- Fatigue
- Fever
- Gastrointestinal bleeding/ hemorrhage
- Gastrointestinal ulcer or ulceration
- Hepatic encephalopathy
- Hepatorenal failure
- Hiccups
- Hypertension
- Hypotension
- Infection (any location)
- Liver failure, acute or chronic
- Lymphopenia
- Malaise
- Mood alteration
- Muscle weakness
- Nausea
- Neutropenia
- Pain (any location)
- Pancreatitis
- Platelet count abnormalities
- Pleural effusion
- Portal hypertension
- Pre-existing chronic liver disease decompensation
- Pulmonary edema
- Pulmonary fibrosis
- Radiation hepatitis
- Radiation induced disease, acute
- Radio Embolization Induced Liver Disease (REILD)
- Sepsis
- Supraventricular arrhythmia
- Thrombosis (arterial or venous)
- Tumor inflammation (including tumor edema)
- Tumor-lysis syndrome
- Vomiting
- Weight loss

Complications related to the administration procedure itself may include:

- Allergic reaction
- Arterial injury including vessel dissection
- Aspiration pneumonia
- Fatigue
- Flushing
- Infection

- Bruising / bleeding / hematoma at site
- Constipation / abdominal distension
- Nausea
- Nerve damage

For the specific adverse events that occurred in the clinical study, please see Section X below.

## IX. SUMMARY OF NONCLINICAL STUDIES

### A. Laboratory Studies

TheraSphere underwent laboratory-based studies that included biocompatibility, engineering/bench, sterility, and packaging/shelf life testing, performed on representative samples of TheraSphere.

#### a. Biocompatibility Testing

The biological suitability of materials constituting the TheraSphere Administration Set was presented in biocompatibility testing for the previously approved HDE (HDE H980006). Testing was performed in accordance with ISO 10993-1, *Biological Evaluation of Medical Devices – Part 1: Evaluation and testing within a risk management process*. All components of the device were found to be biocompatible for their intended use and are summarized in **Table 2** below.

**Table 2: Biocompatibility Tests Performed on TheraSphere Administration Sets**

<b>Test Performed / ISO 10993 Part Number</b>	<b>Test Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
Hemocompatibility / Part 4	To determine potential for hemocompatibility	The device shall not have a substantial effect on partial thromboplastin time, cause a significant drop in platelet counts, or have elevated levels of plasma hemoglobin.	Passed
Cytotoxicity MEM Elution / Part 5	To determine the potential for Cytotoxicity	The test article meets test requirements if none of the cultures treated with the test article show greater than Mild reactivity (Grade 2).	Passed
Guinea Pig Maximization Sensitization / Part 10	To evaluate the allergenic potential or sensitizing capacity	Skin reaction scores received by the test group must be equal or less than the scores received by the negative control group.	Passed

<b>Test Performed / ISO 10993 Part Number</b>	<b>Test Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
Intracutaneous Reactivity / Part 10	To screen test article extracts for potential irritation effects	The requirements of the test are met if the difference between the test article and the control mean score is 1.0 or less (negligible or slight).	Passed
Acute Systemic Injection / Part 11	To screen test article extracts for potential systemic toxic effects	Test is considered negative if none of the animals injected with the test article show a significantly greater biological reaction than the animals treated with the vehicle control.	Passed
Material-Mediated Rabbit Pyrogenicity / Part 11	To screen test article extracts for presence of chemical pyrogens causing a febrile response in rabbits	If no test subject shows an individual rise in temperature of 0.5°C or more above baseline, the test article meets the requirements of the test.	Passed

Extensive information is available concerning the biological safety of TheraSphere Y-90 Glass Microspheres and its components — inert glass microspheres made of well-known elements (yttrium, zirconium, aluminum oxide and silicon dioxide).

**b. Engineering/Bench Testing**

The TheraSphere Y-90 Glass Microsphere System has been tested extensively for safety and functionality. All engineering tests were used to support the HDE approved device (HDE H980006). The following engineering/bench testing was performed and is summarized in **Table 3** below:

- Validation of the septum and vial
- Container closure testing
- Functional validation testing
- Leak pressure and clearance testing

**Table 3: Engineering Testing Performed on TheraSphere**

<b>Test Performed</b>	<b>Test Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
Validation of the septum and vial	To test the effect of the septum, fill volume and crimp pressure on the final device	Meets final product specifications for Y-90 Release, Radionuclidic Purity, Bacterial Endotoxin, and Sterility Inhibition/Enhancement: No inhibition or enhancement shown	Passed

Test Performed	Test Purpose	Acceptance Criteria	Results
		Bacteriostasis/Fungistasis: Meets USP requirements	
Performance Qualification of TheraSphere Crimping System Components	To measure the helium leak rate of septum-sealed vials	<p>Aluminum seal crimp of each vial meets Visual Crimp Inspection</p> <p>Measured helium leak rate of each visually accepted test vial is <math>&lt;10^{-6}</math> cc/sec with full vacuum (<math>\leq 100</math> mTorr) applied across the septum seal</p> <p>Measured helium leak rate of each positive control is <math>\geq 10^{-6}</math> cc/sec with full vacuum (<math>\leq 100</math> mTorr) applied across the septum seal</p>	Passed
Functional Validation Testing of the TheraSphere Administration Set	To test the functionality of the Administration Set and Administration Accessory Kit, and to test delivery performance (percent of radioactive microspheres delivered), safety and ergonomic aspects of the Administration Set and Administration Accessory Kit.	<p><math>\beta</math>-field at catheter inlet during infusion <math>&lt;120</math> R/h; after infusion <math>&lt;200</math> R/h</p> <p><math>\beta</math>-field at operator head position during infusion not detectable</p> <p><math>\gamma</math>-field at operator head position during infusion <math>\leq 10</math> mR/h</p> <p>Pre-infusion setup time <math>&lt;10</math> min</p> <p>Inlet and outlet lines prime successfully</p> <p>Audible “click” is heard/felt and insertion devices cannot be pulled out easily by hand</p> <p>Outlet line is primed; priming valve does not leak during infusion step</p> <p>Relief pressure <math>30 \pm 5</math> psi</p> <p>Leakage resistance <math>&gt;60</math> psi</p> <p>Percent of TheraSphere delivered is <math>&gt;95\%</math></p> <p>No parts cease to function/break during administration and testing</p>	Passed
Leak Pressure and Clearance Testing of TheraSphere	To test the effect of the fill volume, crimp pressure, shelf life, double	<p>Clearance must be <math>\geq 95\%</math> based on a radiation dose rate reduction using a RADOS dosimeter</p> <p>Pressure test must be <math>\geq 60</math> psi</p>	Passed

<b>Test Performed</b>	<b>Test Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
Vials Using Active TheraSphere	autoclaving and elevated irradiation levels on the leak pressure of the septa.	Assessment of any flaking or coring of the septa	

**c. Sterility Testing**

The TheraSphere Yttrium-90 Glass Microspheres final product is terminally steam sterilized in accordance with ISO 17665 *Sterilization of Health Care Products – Moist Heat* and is parametrically released. The TheraSphere Administration Sets are either gamma sterilized in accordance with ISO 11137 *Sterilization of Health Care Products – Radiation* or ethylene oxide sterilized in accordance with ISO 11135 *Sterilization of Health Care Products – Ethylene Oxide*. These tests are summarized in **Table 4** below. The TheraSphere Administration Accessory Kits are re-usable and non-sterile.

**Table 4: Sterility Testing of the TheraSphere Y-90 Glass Microsphere System**

<b>Test Performed / Applicable ISO Standard</b>	<b>Test Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
ISO 17665 <i>Sterilization of health care products – Moist heat</i>	Validation assessment, temperature distribution studies and heat penetration/ biological indicators study	Temperature and pressure during exposure, and cycle time meet specifications  Sterility assurance level (SAL) of minimum 10 <sup>-6</sup>	Passed
ISO 11137 <i>Sterilization of Health Care Products – Radiation</i>	To describe the VD <sub>max</sub> sterilization validation of the device and includes bioburden testing, sterilization administration, sterility testing and LAL testing	The device must withstand the 50 kGy dose without degradation, pass sterility test with <1 positive result, and all areas of carrier must receive minimum dose level of 25 kGy; product must have <20 EU (endotoxin units) per device; bioburden must be <1000 CFUs per device; sterility test with <1 positive result and be negative for bacterio-stasis/fungistasis	Passed

<b>Test Performed / Applicable ISO Standard</b>	<b>Test Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
ISO 11135 <i>Sterilization of Health Care Products – Ethylene Oxide</i>	To demonstrate that the sterilization process and equipment consistently sterilizes the device to a minimum sterility assurance level (SAL) of 10 <sup>-6</sup>  To qualify the minimum heated aeration time needed to meet ISO 10993-7:2008 requirements for EO and EC residual levels	A sterilization load summary showing that the cycle ran within documented specifications; laboratory results showing 100% inactivation of the Biological Indicators; and EO residual results meet requirements of ISO 10993-7:2008	Passed

**d. Packaging / Shelf Life Studies**

TheraSphere® Yttrium-90 Glass Microspheres final product is terminally steam sterilized and is parametrically released. The shelf life of TheraSphere® Y-90 Glass Microspheres is 12 calendar days post-calibration. Packaging testing demonstrated that its design satisfies the requirements for Type A radioactive material packages for transport by air, sea, and ground, as defined by the IAEA *Regulations for the Safe Transport of Radioactive Material, Specific Safety Requirements No. SSR-6, 2012 Edition*. Tests demonstrated the ability of the packaging to withstand the normal and accident conditions of transport by ground, sea, and air for TheraSphere Y-90 Glass Microsphere dose vials. The design and assembly of the packaging meets the requirements of IAEA SSR-6

The packaging and shelf life of the TheraSphere Administration Set was validated using real-time shelf-life testing. The sets sterilized with Gamma irradiation in accordance with ISO 11737 *Sterilization of Health Care Products - Microbiological Methods* have a 1-year shelf life. The sets sterilized using Ethylene Oxide in accordance with ISO 11135 *Sterilization of Health Care Products – Ethylene Oxide* have a 3-year shelf life. The TheraSphere® Administration Accessory Kits are re-usable and non-sterile. The shipping case and shelf life of the TheraSphere Administration Accessory Kit underwent visual and functional inspection and was tested for the intended purpose.

**e. Usability Studies**

TheraSphere was first marketed in the US in 2000, prior to the adoption of standards for usability studies. TheraSphere is in full compliance with Annex C (Evaluation of a User

Interface of Unknown Provenance) of IEC 62366-1:2015 *Medical devices – Part 1: Application of usability engineering to medical devices*.

## **B. Animal Studies**

The safety of TheraSphere was assessed in pre-clinical studies conducted both *in vitro* and on different animal species, including rodents and non-rodents. These pre-clinical studies were reviewed and approved by the FDA in the original HDE application (HDE H980006).

### Study 1 - Chemical Durability of Y<sub>2</sub>O<sub>3</sub>-Al<sub>2</sub>O<sub>3</sub>-SiO<sub>2</sub> (YAS) Glasses for the *in vivo* Delivery of Beta Radiation (2)

In deionized water or saline at 37°C, the weight percent yttrium dissolved from different YAS glasses ranged from only 0.02-0.13% of the total Y present. Overall, and based on their chemical durability, YAS glass microspheres were judged suitable for *in vivo* use.

### Study 2 - Translocation of Yttrium-90 from TheraSphere Glass Spheres Localized in Rat Lungs (Study 6C; data on file)

Radioactive microspheres were delivered into the caudal vein and trapped in the capillaries of the lungs. The activity of the liver, cranial section, caudal section and tail (delivery site) were below the detection limit of the measuring equipment used. The results showed that the delivered radioactivity was accounted for (90%), the percentage of translocation was negligible (<0.1%) and the translocation of Y-90 was independent of time following delivery (within the detection limits of the experiment).

### Study 3 - Effects of <sup>90</sup>Y-Microspheres on Liver Tumors: Comparison of Intratumoral Injection Method and Intra-Arterial Injection (3)

Rats were administered TheraSphere by direct intratumoral injection or intrahepatic arterial injection. The change in tumor size determined by using sonography and the survival time in rats after treatment by each of these methods have been evaluated. Both the intratumoral and the intra-arterial methods resulted in a significant decrease in tumor size and a longer survival time in treating liver tumors, compared with those of the control groups. No significant difference was found in the response rate or survival time between intratumoral treatment and intra-arterial treatment.

### Study 4 - Preliminary Study of the Effects of Radioactive TheraSphere Administration via the Hepatic Artery in Dogs (Study 6E; data on file)

This study determined the radioactivity in the blood of dogs following delivery of TheraSphere via the hepatic artery. All hematologic parameters monitored remained within normal limits as well as the animals' clinical condition, despite elevated serum liver enzymes. This indicated that the amount of Y-90 in circulation in the dogs was extremely small, very near the limits of detection.

#### Study 5 - Effects of Hepatic Arterial Yttrium-90 Glass Microspheres in Dogs (4)

Dogs were administered an injection of non-radioactive TheraSphere into the hepatic artery (up to 12 times the anticipated human dose on a liver weight basis). The injections were well tolerated and produced clinically silent alterations within liver centri-lobular areas and mild to transient increases of alanine aminotransferase (ALT) and alkaline phosphatase (AP) at the highest dose. Dogs receiving high doses of radioactive TheraSphere had elevated but reversible levels of liver enzymes. The portal changes were similar to those observed in humans after external beam therapy. Radiation exposures in excess of 30,000 cGy did not cause total hepatic necrosis and were compatible with survival. No microspheres were found in the bone marrow and no myelosuppression was detected.

#### Study 6 - Clinical Toxicity of Pulmonary Irradiation from Yttrium-90 Glass Microspheres in Dogs (Andrews et al; data on file)

To assist in defining the nature and dose-related potential for radiation-induced pulmonary damage from Y-90 glass microspheres, doses of microspheres were infused into the cephalic vein in dogs to achieve total, uniform lung deposition. All animals were followed clinically for 4 months. In the 3,000 cGy group, no abnormalities were detected by serial chest radiographs, arterial blood gases, or histologic examination of lungs after sacrifice. In addition to development of hypoxemia and respiratory compromise, dogs receiving the higher doses (12,000 and 16,800 cGy) developed changes compatible with radiation pneumonitis and pulmonary fibrosis.

#### Study 7 - Biodistribution of TheraSphere in Rabbits after Hepatic Arterial (HA) Injection (Y-90 Biodistribution; data on file)

This rabbit study involved measurement of the distribution of TheraSphere in organs. TheraSphere was delivered into the hepatic artery of Zealand White rabbits. The study organs were divided into two groups. Those organs that had an arterial supply at or below the celiac axis, which could convey microspheres, were observed to contain some radioactivity. The second group of organs had their arterial supply outside of the celiac axis. No activity was observed in any sample from these organs. The release of Y-90 from TheraSphere appeared to be negligible.

#### Study 8 - Evaluation of Glass Microsphere Delivery in Normal and Tumor Bearing New Zealand White Rabbits (Study 6D; data on file)

Radiation therapy of Y-90 glass microspheres was well tolerated in normal and tumor-bearing rabbits when injected via the hepatic artery. It was concluded that administering glass microspheres to the rabbits' livers does not acutely alter systemic blood pressure or heart rate, nor does it occlude the hepatic capillary bed significantly to induce alterations in regional hepatic perfusion. Glass microspheres tend to be delivered in higher concentrations to central regions of the liver, and to regions with relatively higher local blood flow such as in hepatic tumors.

In summary, the pre-clinical studies showed that TheraSphere has a good response and a long survival time in treating liver tumors, and that Y-90 is not displaced from the glass matrix under clinically relevant conditions.

### **C. Additional Studies**

None

## **X. SUMMARY OF PRIMARY CLINICAL STUDY**

TheraSphere was evaluated in the LEGACY study, a retrospective, single-arm, multi-center study in the US to establish a reasonable assurance of safety and effectiveness of selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter) in patients with unresectable hepatocellular carcinoma (HCC), Child-Pugh score A cirrhosis, well compensated liver function, no macrovascular invasion, and good performance status. As this was a retrospective study, there was no IDE. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

### **A. Study Design**

The LEGACY study was a retrospective, single-arm, multi-center study in adults. Patients in this study received treatment of a single, unresectable HCC lesion  $\leq 8$  cm at the largest diameter with lobar or selective (no more than 2 segments) TheraSphere infusion at a lobar absorbed radiation dose of up to 180 Gray (Gy). Treatment was performed according to site clinical practice. There was no control group for this retrospective, single-arm study.

Patients in the retrospective LEGACY study received their first TheraSphere treatment between 2/13/2014 and 12/22/2017. The database for this PMA reflects data collected through 12/31/2018 and includes 162 patients. Three investigational sites in the US enrolled patients. All consecutively treated patients at each site who met study eligibility criteria were included in the study.

Patients were followed until they met protocol-specified criteria for the end of clinical data collection (i.e., receipt of a non-TheraSphere treatment for HCC in the initial TheraSphere treatment area, death, loss to follow-up) or reached the end of the study on 12/31/2018. All patients were assessed for survival at the end of the study (12/31/2018), irrespective of whether they met criteria for the end of clinical data collection.

Study data were collected as part of usual patient care at each participating institution, and included patient demographics, medical history, disease characteristics, ECOG Performance Status, presence of ascites or encephalopathy, laboratory data, details of TheraSphere treatment, tumor assessment data, and liver volume. Patients were expected to have imaging for tumor assessment available for Month 3 or Month 4 after the initial post-TheraSphere treatment visit, and thereafter at three-month intervals (depending on institutional clinical practice) through 12 months, at six-month intervals at 18 and 24 months, and at 12-month intervals thereafter.

The primary objective of the LEGACY study was to assess the confirmed local tumor control and duration of response (DOR) by localized (within the treatment area) modified Response Evaluation Criteria in Solid Tumors (localized mRECIST) following TheraSphere treatment of solitary, unresectable HCC. The treatment area was defined as the liver volume infused with TheraSphere (perfused liver volume). Radiologic assessments were performed by a Blinded Independent Central Review (BICR) panel.

The LEGACY study was considered a success, if both of the following pre-defined criteria specified by FDA related to the co-primary effectiveness endpoints were met:

- Lower limit of the 95% confidence interval (CI) for confirmed Objective Response Rate (ORR) by localized mRECIST >40%
- Duration of Response (DOR) by localized mRECIST of  $\geq 6$  months in  $\geq 60\%$  of responders.

Localized mRECIST was defined as mRECIST assessment within the treatment area, including the entirety of any tumor either partially or completely within the treatment area. The LEGACY study also assessed ORR and DOR by RECIST 1.1 and mRECIST. Responses were provided separately for localized mRECIST, RECIST 1.1 and mRECIST.

The Treated Population was defined as all enrolled patients. The Per Protocol (PP) Population was defined as all enrolled patients with no pre-defined major protocol deviations (i.e., >10% of TheraSphere not delivered based on residual activity determination, first follow-up tumor imaging >9 months after TheraSphere treatment, last follow-up tumor imaging <12 months after TheraSphere treatment, baseline tumor imaging scan of insufficient quality for BICR review, or baseline imaging assessment by the BICR showing >1 lesion).

All analyses were performed on the 162 patients in the Treated Population. The primary effectiveness endpoint analyses, including sensitivity analyses, were also performed for the 96 patients in the PP Population. Imaging dates were used to programmatically slot imaging assessments into pre-defined evaluation windows.

Baseline was defined as the last non-missing assessment prior to the start of TheraSphere treatment. The treatment area was defined as the perfused volume infused with TheraSphere. Baseline and follow-up images for tumor assessment were uploaded for review by the BICR panel, which evaluated baseline and all available follow-up images for each patient. The BICR panel was blinded to TheraSphere dosing data, clinical outcomes, and subsequent HCC treatments.

For imaging-related effectiveness endpoints, study eligibility criteria required no more than 60 days between baseline imaging and TheraSphere treatment. If baseline tumor imaging was performed >60 days before TheraSphere treatment, confirmatory imaging at the time of angiography was required. Imaging assessments performed after administration of any subsequent HCC treatment within the initial TheraSphere treatment area were not included in computation of the effectiveness endpoints.

A formal sample size computation was not performed for this study. However, a minimum of 100 patients was considered to provide a sufficiently narrow 95% confidence interval (CI) for the ORR as determined by localized mRECIST. It was expected that ORR would be close to 50% using localized mRECIST in the patient population. For an ORR of 50%, the 95% CI would be 40% to 60% with 100 patients and would be 43% to 57% with 200 patients using the methodology of Wilson (5). No formal statistical hypothesis testing was planned or performed for the primary effectiveness analyses.

The ORR was computed as the percent of patients with a complete response (CR) or partial response (PR) by localized mRECIST confirmed at a subsequent visit >4 weeks (30 days) after the date of the first occurrence of CR or PR. If one or more visits subsequent to the first occurrence of CR or PR were missing but a CR or PR was observed at the next visit, then the patient was considered to be a responder for the ORR analysis.

The DOR was computed as the duration between the first response (CR or PR) by localized mRECIST and the first observation of PD using the actual dates of the imaging assessments when the dates of assessment fell within the pre-defined visit window. If PD was not observed for a patient, the computation of DOR used the date of the last imaging assessment within the TheraSphere treatment area before any further HCC treatment within the initial TheraSphere treatment area was administered. If the first occurrence of PD occurred at a delayed imaging assessment (according to the pre-defined evaluation windows), then the middle day of the window was used in the calculation of DOR. Similarly, if one or more consecutive imaging assessments were missed (i.e. no imaging assessments fell within one or more consecutive windows) and the subsequent assessment was the first occurrence of PD, then the day of PD that was used to compute DOR was the middle day of the window for the first missing visit. Only patients with a response (CR or PR) were included in the analysis of DOR. DOR was summarized using descriptive statistics and by Kaplan-Meier (KM) methodology.

Effectiveness analyses of ORR and DOR by RECIST 1.1 and mRECIST were performed in the same manner as the analyses of ORR and DOR by localized mRECIST.

Analyses of the effectiveness endpoints of ORR and DOR were performed for the following subgroups: age group, gender, race, ethnicity, enrolling site, baseline Barcelona Clinic Liver Cancer (BCLC) stage and ECOG Performance Status, HCC etiology, baseline alpha-fetoprotein (AFP) value, baseline tumor size, type of TheraSphere infusion, absorbed dose to perfused liver volume, and fraction of liver treated.

## 1. Clinical Inclusion and Exclusion Criteria

Enrollment in the LEGACY study was limited to patients who met **all** the following inclusion criteria at the time of the first TheraSphere treatment:

- $\geq 18$  years of age
- Confirmed unresectable HCC (by histology or imaging), any etiology
- Has received lobar or selective TheraSphere administration

- Lobar absorbed dose of up to 150 + 20% Gy (180 Gy)
- Child-Pugh (CP) A disease
- BCLC A with ECOG 0 or BCLC C with ECOG 1
- Solitary lesion  $\leq 8$  cm at the largest diameter (the entirety of the tumor will be within the treated region)
- Measurable by mRECIST
- Diagnostic imaging consisting of multi-phase contrast enhanced CT or contrast enhanced MRI within 60 days prior to TheraSphere administration (if >60 days, confirmatory imaging at time of angiography)
- Follow-up imaging consisting of multi-phase contrast enhanced CT or contrast enhanced MRI.

Patients were not permitted to enroll in the LEGACY study if they met any of the following exclusion criteria at the time of the first TheraSphere treatment:

- Prior liver transplantation, surgical resection, locoregional or systemic therapy for HCC
- Any vascular invasion
- Clinically evident ascites or on diuretics for ascites
- Hepatic encephalopathy
- Extrahepatic metastases
- Synchronous diagnosis of additional malignancy other than HCC.

## 2. Follow-up Schedule

This was a retrospective study. After TheraSphere treatment, patients were followed according to site clinical practice.

Preoperatively, patients eligible for enrollment had unresectable HCC confirmed by histology or imaging, diagnostic imaging (multi-phase, contrast-enhanced CT or contrast-enhanced MRI) within 60 days prior to TheraSphere administration or, if >60 days before TheraSphere, confirmatory imaging at the time of angiography and cone-beam CT.

Patients were expected to have follow-up imaging for tumor assessment (i.e., multi-phase contrast-enhanced CT or contrast-enhanced MRI) according to site clinical practice available for Month 3 or Month 4 after the initial post-TheraSphere treatment visit, and thereafter at three-month intervals (depending on institutional clinical practice) through 12 months, at six-month intervals at 18 and 24 months, and at 12-month intervals after 24 months. Baseline and follow-up images for tumor assessment were uploaded for the BICR.

Data on the patients in the LEGACY study were collected as part of usual patient care at each participating institution, and included demographics, medical history, disease characteristics, clinical assessments such as ECOG Performance Status, presence of ascites or encephalopathy, laboratory data, details of TheraSphere treatment such as dosimetry parameters, tumor assessment data, and liver volume.

### 3. Clinical Endpoints

With regards to safety, data on AEs, SAEs, and radiation-specific AEs determined by the investigator to be device-related were assessed. The relationship between absorbed dose to perfused liver volume and the occurrence of related Grade  $\geq 3$  AEs and, separately, the occurrence of related SAEs, was assessed.

With regards to effectiveness, the effectiveness of TheraSphere was evaluated via assessments of ORR and DOR according to localized mRECIST (the co-primary endpoints), RECIST 1.1 and mRECIST.

With regard to success/failure criteria, the study was considered a success if the success criteria for both co-primary effectiveness endpoints were met:

- Lower limit of the 95% CI for confirmed ORR by localized mRECIST  $>40\%$
- DOR by localized mRECIST of  $\geq 6$  months in  $\geq 60\%$  of responders

### **B. Accountability of PMA Cohort**

At the time of database lock, all patients enrolled in the PMA study were available for analysis and the study was complete. Table 5 describes patient disposition

Of the 162 patients in the Treated Population, 106 patients (65.4%) reached the end of clinical data collection (excluding survival follow-up) before the study ended on 31/12/2018. The most common reasons for reaching the end of clinical data collection were receipt of liver transplantation (34 patients, 21.0%), loss to follow-up (23 patients, 14.2%), liver resection (11 patients, 6.8%), and ‘other’ reasons (14 patients, 8.6%). Fifty-six patients (34.6%) were alive and in follow-up through 31/12/2018. All patients, regardless of reason for the end of clinical data collection, were followed for OS through 31/12/2018.

The median duration of follow-up from first TheraSphere treatment (reverse KM estimate) for patients in the Treated Population was 29.9 months (95% CI: 24.7 to 34.6 months).

The most common final study outcomes in the Treated Population were TheraSphere treatment (single or multiple treatments) alone (50 patients, 30.9%) and receipt of liver transplant or resection (43 patients, 26.5%). In total, 45 patients underwent transplantation or resection, including the 43 patients for whom transplantation or resection was a final study outcome and 2 patients for whom transplantation or resection was not the study outcome. Receipt of non-TheraSphere treatment for HCC, excluding liver transplantation or resection, was a study outcome in only 19 patients (11.8%).

**Table 5: Patient Disposition, LEGACY Study, All Screened Patients**

	<b>Patients</b>
<b>Patients Screened</b>	343

	<b>Patients</b>
<b>Populations, n (%)<sup>a</sup></b>	
Treated <sup>b</sup>	162 (47.2%)
PP <sup>c</sup>	96 (28.0%)
<b>Study Status, n (%)<sup>d</sup></b>	
Has data for post TheraSphere treatment follow-up visits been entered?	
Yes	162 (100%)
No	0
<b>End of Study Status, n (%)<sup>d</sup></b>	
Ongoing	56 (34.6%)
Discontinued (i.e., reached the end of clinical data collection [excluding survival follow-up])	106 (65.4%)
Liver transplant	34 (21.0%)
Lost to follow-up	23 (14.2%)
Liver resection	11 (6.8%)
TACE/DEBTACE	8 (4.9%)
Death	7 (4.3%)
Ablation	6 (3.7%)
Chemotherapy	2 (1.2%)
Radiation	1 (0.6%)
Other	14 (8.6%)

<sup>a</sup> Percent is based on number of patients screened.

<sup>b</sup> The Treated Population is defined as all patients enrolled in the study who met all of the inclusion criteria and none of the exclusion criteria.

<sup>c</sup> The PP Population is defined as all patients in the Treated Population without any pre-specified major protocol deviations (i.e., >10% of TheraSphere not delivered based on residual activity determination, first follow-up tumor imaging >9 months after TheraSphere treatment, last follow-up tumor imaging <12 months after TheraSphere treatment, baseline tumor imaging scan of insufficient quality for BICR review, or baseline imaging assessment by the BICR showing >1 lesion).

<sup>d</sup> Percents are based on the number of patients in the Treated Population.

Abbreviations: DEBTACE: drug-eluting bead transarterial chemoembolization; PP: Per Protocol; TACE: transarterial chemoembolization

### **C. Study Population Demographics and Baseline Parameters**

The demographics of the study population in this retrospective study are typical of patients with HCC in the US.

In the Treated Population, the median age was 66 years (range: 21 to 90 years); 42.6% of patients were 18 to <65 years of age, 39.5% were 65 to <75 years of age, and 17.9% were ≥75 years of age.

Most patients were male (75.9%). Race was recorded as white for 49.4% of patients, and ethnicity was recorded as Hispanic or Latino for 8.0% of patients.

The most common medical history items present at baseline were cirrhosis (91%), hepatitis C (69%), hypertension (62%), diabetes (44%), smoking (41%), coronary artery disease (36%), and alcohol abuse (30%).

For most patients in the Treated Population (89.5%), HCC was diagnosed by radiological imaging. The solitary HCC tumors treated in the LEGACY study were most commonly within liver segments VIII (27.2% of patients), VII (24.7% of patients), VI (15.4% of patients), V (14.8% of patients), and IVa (14.2% of patients), as assessed by the study investigator. No patient had satellite lesions identified within the TheraSphere treatment area by the study investigator.

The HCC etiologies in the LEGACY patients were hepatitis C (69%), alcoholic liver disease (30%), non-alcoholic steatohepatitis (14%), hepatitis B (9%), autoimmune hepatitis (2%), and other/unknown (3%, combined). More than one etiology could be recorded for each patient.

At baseline, 60.5% of patients had early HCC (BCLC A), 39.5% had advanced HCC (BCLC C), all patients had CP A score, no patient had encephalopathy, and 98.1% had no ascites on clinical examination or imaging. The distribution of patients across BCLC stages and CP A scores was adequate to allow for meaningful comparisons of study outcomes. Tumor sizes ranged from 0.9 to 8.12 cm at the greatest diameter at baseline (median: 2.649 cm), per the BICR.

#### **D. Safety and Effectiveness Results**

No formal statistical hypothesis testing was planned or performed for the primary effectiveness analyses.

##### **1. Safety Results**

The analysis of safety was based on the 162 patients in the Treated Population. Of the 162 patients in the Treated Population, 106 patients (65.4%) reached the end of clinical data collection (excluding survival follow-up) before the study ended on 31/12/2018. The median duration of follow-up from first TheraSphere treatment (reverse Kaplan-Meier estimate) for patients in the Treated Population was 29.9 months (95% CI: 24.7 to 34.6 months).

##### **Adverse effects that occurred in the PMA clinical study:**

In the Treated Population, 143 patients (88.3%) had a total of 520 AEs. For 139 patients in the Treated Population (85.8%), AEs occurred within 60 days of TheraSphere treatment. Most patients with AEs had Grade 1 events (67.9%), and

91.4% of patients with AEs had one or more events assessed as at least possibly related to TheraSphere or the treatment procedure. No AE caused TheraSphere treatment to be stopped, interrupted, or adjusted. In a dosimetry analysis, there was no impact of absorbed dose to perfused liver volume on the occurrence of device related SAEs. Also, no consistent impact of absorbed doses to perfused liver volume on the occurrence of Grade  $\geq 3$  related AEs was observed.

Fatigue, decreased lymphocyte count, abdominal pain, increased blood bilirubin, nausea, decreased white blood cell count, and decreased platelet count were the most frequent AEs overall (**Table 6**) and the most frequent AEs assessed as at least possibly related to TheraSphere or the treatment procedure (**Table 7**).

As shown in Table 6, in the Treated Population, 130 patients (80.2%) had at least one AE of interest for TheraSphere. The most common AEs of interest for TheraSphere (i.e., those occurring in  $\geq 5\%$  of patients) were fatigue (54 patients, 33.3%), lymphocyte count decreased (46 patients, 28.4%), nausea (28 patients, 17.3%), blood bilirubin increased (24 patients 14.8%), abdominal pain (22 patients, 13.6%), platelet count decreased (19 patients, 11.7%), hypoalbuminemia (14 patients, 8.6%), ascites (13 patients, 8.0%), aspartate aminotransferase increased (11 patients, 6.8%), and abdominal pain upper (10 patients, 6.2%).

As shown in Table 7, approximately 80% of patients had one or more AE assessed as at least possibly related to TheraSphere or the treatment procedure, including 62% of patients in the Treated Population with AEs assessed as at least possibly related to TheraSphere, and 45% of patients with AEs assessed as at least possibly related to the treatment procedure. The AEs related to TheraSphere or the treatment procedure that occurred in  $\geq 5\%$  of patients were similar to the most common AEs overall.

The safety profile of TheraSphere observed in the LEGACY study was consistent with previously observed and reported safety data from clinical trials and marketed use. Most AEs reported in the LEGACY study were not severe or serious in nature, required no invasive intervention, and resolved.

**Table 6: Adverse Events Occurring in  $\geq 5\%$  of Patients with HCC in LEGACY**

Adverse Event	All Grades N=162 n (%)	Grades 3-4 N=162 n (%)
<b>General Disorders</b>		
Fatigue <sup>a</sup>	56 (34.6)	1 (0.6)
<b>Blood and Lymphatic System Disorders</b>		
Lymphocyte count decreased	46 (28.4)	12 (7.4)
White blood cell count decreased	21 (13.0)	1 (0.6)
Platelet count decreased	19 (11.7)	2 (1.2)
<b>Hepatobiliary and Gastrointestinal Disorders</b>		
Blood bilirubin increased <sup>b</sup>	29 (17.9)	3 (1.9)

Blood alkaline phosphatase increased	14 (8.6)	0
AST increased	11 (6.8)	0
Abdominal pain <sup>c</sup>	34 (21.0)	2 (1.2)
Nausea	28 (17.3)	2 (1.2)
Ascites	13 (8.0)	3 (1.9)
Vomiting	13 (8.0)	3 (1.9)
Decreased appetite	13 (8.0)	0
Constipation	9 (5.6)	0
<b>Metabolism and nutrition disorders</b>		
Hypoalbuminemia	14 (8.6)	1 (0.6)
Hyperglycemia	11 (6.8)	0
<b>Musculoskeletal and connective tissue disorders</b>		
Musculoskeletal pain <sup>d</sup>	9 (5.6)	2 (1.2)

<sup>a</sup>Includes asthenia

<sup>b</sup>Includes hyperbilirubinemia

<sup>c</sup>Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, and epigastric discomfort

<sup>d</sup>Includes back pain, myalgia, neck pain, and pain in extremity

**Table 7: Related Adverse Events Occurring in  $\geq 5\%$  of Patients with HCC in LEGACY**

Adverse Event	All Grades N=162 n (%)	Grades 3-4 N=162 n (%)
<b>General Disorders</b>		
Fatigue <sup>a</sup>	54 (33.3)	1 (0.6)
<b>Blood and Lymphatic System Disorders</b>		
Lymphocyte count decreased	46 (28.4)	12 (7.4)
White blood cell count decreased	16 (9.9)	1 (0.6)
Platelet count decreased	14 (8.6)	2 (1.2)
<b>Hepatobiliary and Gastrointestinal Disorders</b>		
Blood bilirubin increased <sup>b</sup>	24 (14.8)	2 (1.2)
Blood alkaline phosphatase increased	14 (8.6)	0
AST increased	10 (6.2)	0
Abdominal pain <sup>c</sup>	29 (17.9)	2 (1.2)
Nausea	24 (14.8)	2 (1.2)
Ascites	10 (6.2)	2 (1.2)
Vomiting	11 (6.8)	3 (1.9)
Decreased appetite	11 (6.8)	0
<b>Metabolism and nutrition disorders</b>		
Hypoalbuminemia	9 (5.6)	0

<sup>a</sup>Includes asthenia

<sup>b</sup>Includes hyperbilirubinemia

<sup>c</sup>Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, and epigastric discomfort

Most non-serious AEs reflecting abnormal laboratory values were Grade 1 or 2 events. These laboratory abnormalities did not contribute to the development of additional AEs such as jaundice, bleeding, or infection. There was a single occurrence of a Grade 4 abnormal laboratory value, platelet count decreased, which occurred in a patient with pre-existing thrombocytopenia. This event did not require any intervention. The patient underwent liver transplantation approximately 2.8 months after a single treatment with TheraSphere.

At baseline, 109 patients in the Treated Population (67.3%) had abnormal low platelet and/or high INR values, and 38 patients (23.5%) had abnormal low leukocyte values. Most abnormal platelet, INR and leukocyte values were Grade 1 abnormalities. No increase in frequency of bleeding or infection events was observed in these patients. Nineteen patients in the Treated Population died, including 12 patient deaths due to disease progression, 5 deaths with cause not specified, 1 death due to multi-organ failure, and 1 death due to an SAE, cerebral vascular accident, which occurred 66 days after the most recent TheraSphere treatment.

Twenty-two SAEs were recorded for 16 patients. Nine of these patients experienced 11 SAEs assessed as at least possibly related to TheraSphere. No SAE assessed as related to TheraSphere led to the death of a patient.

The SAEs that occurred in more than one patient in the Treated Population were vomiting and pneumonia (each in 3 patients, 1.9% each), and abdominal pain, ascites and nausea (each in 2 patients, 1.2% each).

#### AEs related to dose

A dosimetry analysis showed no statistically significant impact of any covariate on the occurrence of SAEs or Grade  $\geq 3$  AEs assessed as at least possibly related to TheraSphere or the treatment procedure.

#### AEs in specific populations

In the 109 patients with low baseline platelet counts and/or high baseline INR values, 9 patients had a bleeding event; these included 1 SAE (gastrointestinal hemorrhage) and 8 non-serious events. In 38 patients with low baseline white blood cell count values, 3 patients had an infection event; these included 1 SAE (lung infection) and 2 non-serious events.

## 2. Effectiveness Results

The analysis of effectiveness was based on the 162 patients in the Treated Population. Of the 162 patients in the Treated Population, 106 patients (65.4%) reached the end of clinical data collection (excluding survival follow-up) before the study ended on 12/31/2018. The median duration of follow-up from first TheraSphere treatment (reverse Kaplan-Meier estimate) for patients in the Treated

Population was 29.9 months (95% CI: 24.7 to 34.6 months). Efficacy results for ORR and DOR are summarized in Table 8.

**Table 8: Objective Response Rate (ORR) and Duration of Response (DOR), LEGACY Study**

	Treated Population N=162		
	Localized mRECIST	mRECIST	RECIST 1.1
<b>ORR per BICR, n (%)</b>	117 (72.2%)	111 (68.5%)	75 (46.3%)
(95% CI) <sup>a</sup>	(64.9, 78.5)	(61.0, 75.2)	(38.8, 54.0)
Complete Response (CR)	115 (71.0%)	109 (67.3%)	11 (6.8%)
Partial Response (PR)	2 (1.2%)	2 (1.2%)	64 (39.5%)
<b>DOR per BICR</b>			
Range (months) <sup>b,c</sup>	1.5 <sup>+</sup> , 48.1 <sup>+</sup>	1.5 <sup>+</sup> , 48.1 <sup>+</sup>	1.5 <sup>+</sup> , 45.1 <sup>+</sup>
Percent with duration $\geq$ 6 months <sup>d</sup>	76.1%	74.8%	72.0%

<sup>+</sup> Indicates response was ongoing at the time stated

<sup>a</sup> 95% CI for percentage of patients with ORR per BICR, based on the methodology of Wilson (1927)

<sup>b</sup> Months = (Date of first PD - Date of first CR or PR + 1)/30.4375. If no PD occurred, the date of the last imaging assessment within the treatment area, before any further HCC treatment was administered, was used.

<sup>c</sup> Median duration of response by Kaplan Meier analysis not reached with a median follow-up duration of approximately 30 months.

<sup>d</sup> Percents are based on the number of patients with confirmed CR or PR.

Note: Localized mRECIST is defined as mRECIST assessment within the treatment area, including the entirety of any tumor that is either partially or completely within the treatment area; the treatment area is the perfused volume infused with TheraSphere. Responses are defined as a patient with CR or PR that is confirmed at a subsequent visit >4 weeks (30 days) after the date of the first occurrence of CR or PR. Any assessments performed subsequent to the administration of any further HCC treatment within the initial TheraSphere treatment area are excluded. Patients who received non-TheraSphere treatment outside of the initial treatment areas before the confirmatory scan for response assessment was performed are not excluded from the mRECIST (N=2) and RECIST 1.1 (N=4) analysis.

Abbreviations: BICR: blinded independent central review; CI: confidence interval; mRECIST: modified Response Evaluation Criteria in Solid Tumors; PD: progressive disease

Both co-primary effectiveness endpoints prespecified by FDA were met in the LEGACY study. Key effectiveness results include:

- The ORR by localized mRECIST per the BICR was 72.2% (95% CI: 64.9, 78.5)
- The DOR by localized mRECIST per the BICR was  $\geq 6$  months in 76.1% of responders.
- The ORR was 46.3% and the DOR was  $\geq 6$  months in 72.0% of responders by RECIST 1.1.
- The ORR was 68.5% and the DOR was  $\geq 6$  months in 74.8% of responders by mRECIST.

FDA considers these rates acceptable as they meet FDA's prespecified criteria. Possible selection bias, results possibly not generalizable to centers with less experience with this device, and tumor size skewed to the lower end of the range (range up to 8 cm, median size 2.6 cm) are present.

TheraSphere has not been shown to prolong survival in adequate and well-controlled trials. There is no evidence supporting the use of systemic therapy in combination with TheraSphere. There were insufficient data for patients with tumors 5 – 8 cm in diameter (N=9; ORR by localized mRECIST of 66.7%; 95% confidence interval: 35.4%, 87.9%) to draw a conclusion regarding effectiveness or safety, even though tumors of this size are being included in the indication for use.

#### Use in the geriatric population

The LEGACY study included 64 (40%) patients 65 to <75 years of age and 29 (18%) patients  $\geq 75$  years of age. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

#### Dosimetry

Perfused liver volume was determined by post Y-90 SPECT/CT bremsstrahlung (N=51) and/or CBCT diagnostic (N=104) imaging and was unique for each patient within the LEGACY study. In seven patients, the perfused liver volume was not evaluable.

Table 9 provides the median perfused liver volume and median absorbed dose to perfused liver volume (Gy) by perfused liver volume quartiles. Patients with a subsegmental or segmental perfused liver volume (up to two segments) were within the 1st to 3rd quartiles, while the 4th quartile contained both segmental (N=27) and lobar perfused volumes (N=11). The median perfused liver volume and absorbed dose to perfused liver volume for the full cohort are also listed in Table 9.

#### **Table 9: Perfused Liver Volume (cm<sup>3</sup>) and Absorbed Dose to Perfused Liver Volume (Gy) by Quartile and Full Cohort**

	<b>1<sup>st</sup> Quartile (N=39)</b>	<b>2<sup>nd</sup> Quartile (N=39)</b>	<b>3<sup>rd</sup> Quartile (N=39)</b>	<b>4<sup>th</sup> Quartile (N=38)</b>	<b>Full Cohort (N=155)</b>
<b>Perfused liver volume (cm<sup>3</sup>) Median (Range)</b>	62 (19 – 91)	121 (92 – 155)	200 (158 – 262)	459.5 (271 – 1363)	155.0 (19 – 1363)
<b>Absorbed dose to perfused liver volume (Gy) Median (Range)</b>	927 (188 – 2980)	518 (147 – 1313)	410 (122 – 1025)	146 (70 – 396)	410.1 (70 – 2980)

Note: Seven patients did not have an absorbed dose to perfused volume

### Histopathologic analysis

Histopathologic analysis to determine degree of necrosis was evaluated by individual institutions for patients who underwent transplant or resection (N=45) following TheraSphere treatment. A total of 20 patients underwent transplant or resection prior to objective response assessment (N=11) or prior to confirmation of objective response (N=9). Table 10 summarizes the histopathologic response for patients who achieved a complete response by objective response assessment in those patients that underwent a transplant or resection.

**Table 10: Histopathology Response**

<b>Imaging Response</b>	<b>Histopathology Response</b>
CR (N=25)	Complete (N=16)
	Extensive (N=6)
	Partial (N=3)

Abbreviation: CR: Complete Response

Note: Degree of Necrosis, as determined by site investigators: Complete = 100% necrosis (no viable tumor); Extensive = 50-99% necrosis (significant necrosis with presence of minimal viable tissue); Partial = minimal necrosis (encompassing <50% of the treated tumor)

### 3. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

## **E. Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included three (3) site Principal Investigators and one (1) Global Principal Investigator, of which none were full-time or part-time employees of the sponsor and one (1) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) as described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

## **XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION**

TheraSphere has been marketed commercially in the United States under HDE H980006 since 2000. Over 20,000 patients have been treated in the US, with an additional >10,000 patient administrations outside the US. All adverse events received since commercial distribution of TheraSphere in the US have been summarized in the HDE annual reports. Between 07/01/2012 and 12/31/2019, >75,000 commercial TheraSphere dose vials were shipped worldwide. In that time, 302 AE reports were received by the company from reports in the field or in the published medical literature. This is an AE reporting rate of 0.4% of the total number of dose vials shipped to date. Of the AEs received, most have either been reported as product complaints or were identified in the published medical literature. The most frequently reported serious adverse events were hepatic failure, disease progression and ascites; the most frequently reported non-serious adverse events were fatigue, abdominal pain, increase in blood bilirubin and ascites. These are consistent with the AEs observed in the LEGACY study.

## **XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION**

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Radiology Panel, an FDA advisory committee, for review and recommendation.

## **XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

In the LEGACY study, 117/162 patients (72.2%) had a confirmed response (CR or PR) by localized mRECIST; of those 117 patients, 89 (76.1%) had a duration of response  $\geq 6$  months. TheraSphere has not been shown to prolong survival in adequate and well-controlled trials, but met the prespecified endpoints for local control: a lower limit of the 95% confidence interval (CI) for confirmed Objective Response Rate (ORR) by localized mRECIST >40% and a DOR by localized mRECIST of  $\geq 6$  months in  $\geq 60\%$  of responders. In the LEGACY study there were no meaningful outcome differences by age, sex/gender, race, and ethnicity that impacted the effectiveness or safety of the device. TheraSphere should be used in unresectable HCC patients with liver-only disease. There is no evidence supporting the use of systemic therapy in combination with TheraSphere.

## **B. Safety Conclusions**

Since the LEGACY pivotal study was retrospective, it is not possible to be certain that all SAEs and AEs were captured. However, the risks of the device are based on clinical laboratory and animal studies, 20 years of clinical use in >30,000 patients globally (including >20,000 patients in the US under HDE H980006), in addition to the data collected in the LEGACY study conducted to support PMA approval as described above. In the LEGACY study, 88% of patients (88.3%) had AEs. Most AEs occurred within 60 days of TheraSphere treatment. Most patients (68%) with AEs had Grade 1 events. Fatigue, decreased lymphocyte count, abdominal pain, increased blood bilirubin, nausea, decreased white blood cell count, and decreased platelet count were the most frequent AEs overall. Most AEs reported in the LEGACY study were not severe or serious in nature, required no invasive intervention, and were resolved. Twenty-two SAEs were recorded for 16/162 patients. Nine of these patients experienced 11 SAEs assessed as at least possibly related to TheraSphere. The SAEs that occurred in more than one patient in the LEGACY study were vomiting and had pneumonia (3 patients each), and had abdominal pain, ascites and nausea (2 patients each). No SAE assessed as related to TheraSphere led to the death of a patient. The safety profile of TheraSphere observed in the LEGACY study was consistent with previously observed and reported safety data from clinical trials and marketed use.

## **C. Benefit-Risk Determination**

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The benefit is local control of tumor in patients with unresectable disease. In the LEGACY study, 72% of patients had a confirmed response (CR or PR) by localized mRECIST; of those patients, 76% had a duration of response  $\geq 6$  months. Both of these exceed the prespecified criteria.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Additionally, the probable risks are based on 20 years of clinical use in >30,000 patients globally (including >20,000 patients in the US under HDE H980006). In the LEGACY study, 88% of patients (88.3%) had AEs, most of which occurred within 60 days of TheraSphere treatment, and most of which were Grade 1 events. A SAE occurred in 10% of patients; the SAEs that occurred in more than one patient in the LEGACY study were vomiting and pneumonia (3 patients each), and abdominal pain, ascites and nausea (2 patients each). No SAE assessed as related to TheraSphere led to the death of a patient.

Additional factors to be considered in determining probable risks and benefits for the TheraSphere device included the retrospective, single-arm nature of the LEGACY study, with resultant uncertainty in adequacy of reporting adverse events. This was balanced by the data derived from 20 years of clinical use in >30,000 patients globally (including >20,000 patients in the US under HDE H980006). In that time, 302 AE reports were received by the company from reports in the field or in the published

medical literature. Of the AEs received, most have either been reported as product complaints or were identified in the published medical literature. The most frequently reported serious adverse events were hepatic failure, disease progression and ascites; the most frequently reported non-serious adverse events were fatigue, abdominal pain, increase in blood bilirubin and ascites. These are consistent with the AEs observed in the LEGACY study.

The results of the study are likely generalizable to the US population of patients with unresectable HCC confined to the liver, Child-Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status, as all of the LEGACY subjects were US patients, and all consecutively treated patients at each site who met study eligibility criteria were included in the study.

1. Patient Perspective

This submission did not include specific information on patient perspectives.

In conclusion, given the available information above, the data support the use of TheraSphere as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable hepatocellular carcinoma (HCC), Child-Pugh score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status, and the probable benefits outweigh the probable risks.

**D. Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The effectiveness outcomes in the LEGACY study exceeded FDA's prespecified criteria for ORR and DOR, and the risk analysis was consistent with the risks observed in 20 years of use in >30,000 patients globally (including >20,000 patients in the US under HDE H980006).

**XIV. CDRH DECISION**

CDRH issued an approval order on March 17, 2021. The final clinical conditions of approval cited in the approval order are described below. A post approval study is needed. It is a prospective clinical study to provide sufficient data for reasonable calculation of radiation-absorbed dose to the whole body and irradiated critical organs.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

**XV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## **XVI. REFERENCES**

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