

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
300 Boston Scientific Way
Marlborough, MA 01752

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200029/S011

Date of FDA Notice of Approval: February 10, 2026

The original PMA (P200029) was approved on March 17, 2021, and 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. The SSED supporting the original indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to update the device labeling to include a new dosimetry method, the multicompartiment dosimetry (MCD) method, which allows separate evaluation of microsphere dose to the patient for the target (i.e., tumor) and healthy tissue.

II. INDICATIONS FOR USE

TheraSphere are 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 are contraindicated in patients:

- whose Tc-99m macroaggregated albumin (^{99m}Tc-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 0.61 GBq (16.5 mCi) 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,O₂) of < 60 mmHg, or oxygen saturation (Sa,O₂) of < 90 %).
- with portal vein thrombosis (PVT) Type 4 involvement and lack of ^{99m}Tc-MAA deposition on the PVT seen on the ^{99m}Tc-MAA imaging.
- with > 70 % tumor replacement in the liver.
- who have severe liver dysfunction, including hepatic encephalopathy, clinically evident ascites, or treatment with diuretics for ascites.
- 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.

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the TheraSphere labeling.

V. **DEVICE DESCRIPTION**

TheraSphere consist of insoluble glass microspheres, with sphere diameter of 15 to 35 µm, 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). The microspheres are delivered into the liver tumor through a microcatheter placed into the hepatic artery branch that supplies blood to the tumor. The 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 microspheres diminishes substantially over the first 2 weeks after treatment. The microspheres remain permanently implanted in the liver tissue.

TheraSphere (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 ±10 % of nominal activity. 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.

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.

The MCD method is used to perform pretreatment and post-treatment Y-90 dosimetry to determine either perfused volume absorbed dose or tumor and normal tissue absorbed dose. The alternative is single compartment dosimetry (SCD), typically used in ablative radioembolization.

There are several other alternatives for management of HCC. Each alternative 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 received FDA approval under PMA P200029 in 2021 and were previously marketed commercially under HDE H980006 since 2000. TheraSphere has been marketed in Canada (2005), Europe (2006), the Middle East (2009), Asia (2015) and Latin America (2018). TheraSphere has not been withdrawn from commercial distribution (marketing) in any country for any reason related to safety and effectiveness. The current supplement was submitted to update the device labeling to include a new dosimetry method, MCD, which was not included in prior US labeling.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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. Potential adverse events (AEs) which may be associated with the use of TheraSphere in the treatment of HCC usually occur within the first 4 to 6 weeks after treatment.

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device and Y-90 microspheres based on clinical trial data, literature reviews and post market surveillance:

- Allergic reaction (contrast or other)
- Anorexia
- Arrhythmia (e.g. supraventricular arrhythmia)
- Ascites

- Aspiration pneumonia (procedure related)
- Bile Duct injury
- Bleeding/hemorrhage
- Chills / rigors
- Cholangitis
- Cholecystitis
- Cognitive changes (i.e. mood alteration, anxiety)
- Colitis
- Death
- Dehydration
- Dizziness
- Edema including pulmonary edema
- Electrolyte abnormalities
- Fall
- Fatigue/muscle weakness
- Fever
- Flushing (procedure related)
- Gastrointestinal bleeding
- Gastrointestinal symptoms (e.g. abdominal distention, constipation, diarrhea, nausea, vomiting)
- Gastrointestinal ulcer and ulceration
- Hematologic cytopenia (e.g. anemia, lymphopenia, neutropenia, thrombocytopenia)
- Hematoma
- Hepatic dysfunction
- Hepatic encephalopathy
- Hepatic failure
- Hiccups
- Hypertension
- Hypotension
- Infection/abscess/sepsis
- Malaise
- Need for additional intervention or surgery
- Nerve damage (procedure related)
- Pain/discomfort
- Pleural effusion
- Portal hypertension
- Post-embolization syndrome (PES)
- Pulmonary fibrosis
- Radiation exposure (unintended)
- Radiation induced disease (i.e., fibrosis, gastritis, esophagitis, pneumonitis, pancreatitis, ulceration)
- Radio Embolization Induced Liver Disease (REILD)
- Renal insufficiency/failure (elevated BUN/creatinine)
- Respiratory distress/insufficiency/failure/dyspnea
- Thrombosis/thrombus
- Tumor inflammation (including tumor edema)
- Tumor-lysis syndrome
- Vessel trauma (e.g. dissection, injury, pseudoaneurysm, perforation, rupture)
- Weight loss

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

IX. SUMMARY OF NON-CLINICAL STUDIES

All non-clinical laboratory studies are included as part of the original PMA P200029 and subsequent supplements. Refer to the P200029 TheraSphere SSSED available on the FDA website.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

To support and establish a reasonable assurance of safety and effectiveness regarding the MCD device labeling expansion, data from two clinical studies was leveraged: DOSISPHERE (prospective) and TARGET (retrospective). The former study provided primary support for the labeling expansion, whereas the latter study was considered secondary and supportive of the primary study. A summary of the clinical studies is presented below.

DOSISPHERE Study

A. Study Design

The study was a randomized, prospective, multicenter, open-label phase 2 study in adult patients with unresectable HCC. Patients were treated between December 2015 and January 2018. Patients from 4 investigational sites were randomized (intention to treat (ITT) population) to receive SIRT using either SCD or MCD.

The primary objective of the study was to evaluate the safety and effectiveness of MCD as compared to SCD for SIRT with TheraSphere in patients with HCC. The primary endpoint assessment was the imaging tumor response of the index lesion (tumor with largest diameter) at 3 months evaluated by site investigator using EASL. The 6-week and 3-month CT scan response assessments were centrally reviewed by two masked central reviewers to confirm the primary endpoint results. Safety was assessed in all patients who received at least one SIRT and was analyzed based on the randomization arm (modified intention-to-treat population (mITT) population).

The dosimetry goal for patients in the SCD arm was to deliver a perfused liver volume absorbed dose of 120 ± 20 Gy. The dosimetry goal for patients in the MCD arm was defined as targeting the index lesion with a tumor absorbed dose (TAD) of ≥ 205 Gy (exceeding 250-300 Gy if possible) while keeping the normal perfused liver dose < 120 Gy with a hepatic reserve¹ of 30%. An absorbed dose to treated healthy liver could exceed 120 Gy where the hepatic reserve was $> 30\%$. The SCD arm was the control group.

Patients in the study received their first SIRT 1-2 weeks post ^{99m}Tc-MAA simulation scan, and for bilobar patients a second treatment could be performed 5-8 weeks thereafter to the untreated lobe (maintaining the minimum 30% hepatic reserve over the 2 treatments). Subjects were followed up until disease progression or death. Follow-up visits were scheduled at 4-6 weeks after SIRT, and at 3, 6, and 12 months.

¹ Hepatic reserve is the fraction of functional liver that will not receive Y-90.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the study was limited to patients who met the following inclusion criteria:

- Patients ≥ 18 years of age and willing and able to provide written informed consent
- Histologically confirmed HCC not amenable to surgery or local ablative treatment
- Barcelona Clinic Liver Cancer (BCLC) A, B or C classification
- At least one lesion ≥ 7 cm
- Non-treated liver parenchyma of $\geq 30\%$ after the first TheraSphere treatment
- Unilobar liver disease (with bilobar patients included only if one of the two lobes presented minimal involvement with segmental approach possible and hepatic reserve $\geq 30\%$ after two SIRT)
- Child-Pugh (CP) liver function class A or B7 if bilirubin < 35 $\mu\text{mol/L}$
- Eastern Cooperative Oncology Group (ECOG) 0 or 1
- Hemoglobin ≥ 8.5 g/dL, granulocyte counts $\geq 1,500/\text{mm}^3$, platelet counts $\geq 50,000/\text{mm}^3$, bilirubinemia < 35 $\mu\text{mol/L}$ transaminases ≤ 5 times the upper limit of normal (ULN), serum creatinine ≤ 1.5 times the ULN
- Expected survival greater than 12 weeks
- Approved method of contraception and negative pregnancy test for women of child-bearing age
- Delay of at least 4 weeks between previous sorafenib treatment (if applicable) and the diagnostic angiography.

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

- Patients presenting the following contraindications to SIRT at the $^{99\text{m}}\text{Tc}$ -MAA scintigraphy: high pulmonary shunting (leading to pulmonary dosimetry > 30 Gy); gastrointestinal (GI) shunt not correctable with embolization; poor tumor uptake (no increased tumor uptake even after more selective administration) or poor PVT uptake; or Main PVT without $^{99\text{m}}\text{Tc}$ -MAA targeting.
- Technical failure at diagnostic angiography
- HCC that was operable or amenable to local ablative treatment (e.g. radiofrequency)
- History of hepatectomy, unless segmental treatment is considered, with hepatic reserve $\geq 30\%$ after SIRT
- Previous treatment with sorafenib, unless the treatment was stopped at least 4 weeks prior to the diagnostic angiography
- History of chemoembolization of the main lesion (except for a nodular residual lesion measuring at least 7 cm, or progression after initial response)
- Bilateral involvement with a hepatic reserve after treatment $\leq 30\%$
- Cancer progressing or treated within the previous 1 year

- Extrahepatic spread (other than to the lymph nodes of the hilum, with a lesion < 2 cm)
- More than 70% of the liver with tumor involvement
- Bilirubin ≥ 35 $\mu\text{mol/L}$
- Severe underlying biliary disease: a) bile duct abnormality (stent, dilation), b) cirrhosis of biliary origin
- Women of child-bearing age who were not using an approved method of contraception or who presented a positive blood pregnancy test at the screening visit

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations between 4-6 weeks after the first SIRT procedure, followed by examinations at Months 3, 6 and 12.

A list of all assessments and data collected at each study timepoint is provided in Table 1 below.

Table 1. DOSISPHERE Schedule of Visits and Assessments

	D-28 to D-7	D-21 to D-7	D-14 to D-7	D1 ³	W4 to W6	W5 to W8			
	Screening	Inclusion ¹ (if applicable)	Simulation 1 Randomization	Treatment 1	Follow-up of treatment 1 Simulation 2 (if applicable)	Treatment 2 (if applicable)	M3 ±4 days	M6 ±1 week	M12 ¹⁰ ±1 week
Informed consent	X ^a								
Clinical examination	X	X		X ⁴	X	X ⁴	X	X	X
Chest-abdomen CT-scan*	X				X		X	X	X
Pregnancy test*	X								
Blood test*	X	X		X ⁴	X	X ⁴	X	X	X
Liver function test*	X	X		X ⁴	X	X ⁴	X	X	X
Electrolytes*	X	X		X ⁴	X	X ⁴			
Kidney function test*	X	X		X ⁴	X	X ⁴	X	X	X
Alpha-fetoprotein level*	X	X		X ⁴	X	X ⁴	X	X	X
Monitoring blood sample ⁵	X				X	X			
CT volumetry*	X								
Diagnostic angiography			X ²		X ⁶				
Hepatic perfusion scintigraphy, dosimetry analysis, and determination of activity to be injected			X ²		X ⁶				
Therapeutic angiography, TheraSphere® injection				X		X ⁷			
Post-therapeutic scintigraphy and dosimetry				X		X ⁷			
Response evaluation					X		X	X	X
Survival evaluation					X		X	X	X
Collection of AEs/SAE - tolerance follow-up	X	X	X	X	X		X	X	X ⁹
Monitoring of concomitant treatments ⁸	X	X			X		X	X	X ⁹

D: Day; M: Month; W: Week.

a : The informed consent could be signed up to 6 weeks before the simulation.

* : If subjects have had a CT-scan and laboratory work-up before signing the written informed consent, the results of these tests could be used provided the following delays were respected: 1 week maximum between laboratory work-up and simulation; 4 weeks maximum between CT-scan and treatment.

* : Local evaluations and centralized review for the tests at screening, at Week 4-6, and at Month 3.

1 : Optional visit to be conducted if the interval between the screening visit and the simulation was more than 1 week.

2 : The diagnostic angiography/scintigraphy was performed following inclusion of the subject (maximum of 1 week later) and preceded randomization (local evaluation and centralized review).

3 : Treatment was done a maximum of 1 to 2 weeks after simulation (preferably 1 week), and a maximum of 4 weeks after the screening visit.

4 : Clinical examination and laboratory work-up done the day before or the morning of the treatment. The results had to be available before the treatment for validation of inclusion criteria (laboratory work-up parameters).

5 : Monitoring blood samples taken during the visit at screening, 6 weeks, and 3 months after the first treatment. At each visit, a plasma tube was to be collected and stored for exploratory analyses.

6 : In case of a 2nd injection: the diagnostic angiography/scintigraphy was done during the 1st follow-up visit after the 1st administration (local evaluation and centralized review).

7 : The therapeutic angiography/scintigraphy for the 2nd administration was done between 1 and 2 weeks (preferably 1 week)

after the 2nd diagnostic angiography/scintigraphy (local evaluation and centralized review).

8 : Treatments taken by the subjects 30 days before and/or ongoing at the time of selection were collected for the study.

9 : The data were collected up to 4 weeks after the end of treatment, if applicable (6 months in the case of hepatotoxicity or SAE follow-up).

10 : After M12, the subject completed the study and standard follow-up was resumed. Data on vital status, lesion recurrence, and start of new antineoplastic treatments were collected every 3 months.

3. Clinical Endpoints

With regards to safety, AEs were collected throughout the subjects' study duration, and their severity and toxicity evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.03.

With regards to effectiveness, TheraSphere treatment using MCD or SCD was evaluated via assessment of tumor response (complete or partial) of the index lesion at 3 months post SIRT treatment (evaluated by the site investigator using EASL criteria).

With regard to success/failure criteria, success for the primary effectiveness endpoint was defined as improvement of 35% in the tumor response rate in the personalized dosimetry (MCD) group as compared with the standard dosimetry (SCD) group, with a hypothesis of a 50% response rate in the standard dosimetry group, a 2.5% one-sided type I error rate and 80% power. The sample size could vary and the study interrupted based on pre-specified statistical criteria and based on the level of conditional power (estimated difference in the response rate) attained at interim analysis: (1) If the estimated difference in the response rate was >15% and the one-sided p value was <0.01348 at the interim analysis, the study could be stopped and concluded as positive; (2) If the estimated difference in the response rate was <15%, the trial was to be stopped early for futility reason; or (3) if the estimated difference in the response rate was >15% but the difference in response rate was not statistically significant, the trial was to be continued and the sample size was to be increased.

B. Accountability of PMA Cohort

At the time of database lock, 93 subjects had been screened, of whom 60 subjects were found to be eligible, and 56 subjects were randomized and treated (28 in each group according to planned treatment). An interim analysis on the primary endpoint was conducted on the total of 56 treated subjects (100%). This interim analysis was also the study completion as the results met the prespecified stopping criteria and the study was interrupted for efficacy.

Of the 93 patients screened for the study, 33 were considered screen failures (19 patients did not meet entry criteria, and an additional 14 patients were considered screen failures after the pretreatment diagnostic angiography and ^{99m}Tc-MAA hepatic perfusion scintigraphy). A total of 60 patients were randomized and comprised the intent to treat (ITT) population. Of the 60 patients in the ITT population, 56 patients (93%) received TheraSphere treatment. There were 4 patients who did not receive

treatment due to major protocol deviations (e.g., not meeting eligibility criteria) that were identified after randomization but before treatment. These 4 patients were excluded from the mITT population, therefore the mITT population comprised 28 patients (90%) in the MCD treatment arm and 28 patients (97%) in the SCD arm received treatment.

Of the 28 patients in the MCD arm, 25 (89%) completed the Month 3 visit and 10 (36%) reached the end of the 12-month follow-up period. In the SCD arm, 23 (82%) completed the Month 3 visit and 5 (18%) reached the end of the 12-month follow-up period. The most common reason for study discontinuation post treatment was progressive disease (MCD: 16 (57%), SCD: 20 (71%)), resection (MCD: 10 (36%), SCD: 1 (4%)), death (MCD: 2 (7%), SCD: 1 (4%)) and other (MCD: 0, SCD: 2 (7%)). All patients regardless of reason for the end of clinical data collection were followed for OS through December 2018. Subsequent to treatment in this study, 10/28 patients (36%) in the MCD arm went on to undergo curative resection; 1/28 (4%) of patients in the SCD underwent a resection (p=0.0025).

This study includes subjects which extend beyond the indicated population. Notably, DOSISPHERE did not restrict tumor size within the labeled diameter, was not limited to solitary tumors, included Child-Pugh Score B7 cirrhosis, and allowed patients with tumor vascular invasion. From the DOSISPHERE study population (28 patients in each arm), only one patient in each arm met the current labeling indication.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for patients with intermediate or advanced unresectable HCC in the US, but the baseline characteristics are representative of patients who have more extensive disease and are sicker than those indicated in the Indications for Use.

Baseline characteristics are summarized in Table 2 below.

Table 2: DOSISPHERE study baseline characteristics, mITT Population (Treated Patients)

Baseline Characteristics	mITT population (Treated patients)	
	MCD (N = 28)	SCD (N = 28)
Median age, years (range)	65.5 (39-86)	63.0 (18-84)
BCLC B/C, n (%)	3 (11) / 25 (89)	2 (7) / 26 (93)
Child Pugh A5 / A6-B7, n (%)	22 (79) / 6 (21)	22 (79) / 6 (21)
Portal vein invasion, n (%)	18 (64)	21 (75)
HCC, n (%) Solitary/Multifocal	15 (54) / 13 (46)	12 (43) / 16 (57)
Tumoral involvement (%) Mean $\pm$ STD	23.01 $\pm$ 13.96	25.69 $\pm$ 14.19
Index tumor size (cm) Mean $\pm$ STD	10.36 $\pm$ 2.44	10.67 $\pm$ 2.79

Abbreviations: BCLC: Barcelona Clinic Liver Cancer, ECOG: Eastern Cooperative Oncology Group; HCC: hepatocellular carcinoma, (m)ITT: (modified) intent-to-treat; MCD: multicompartiment dosimetry; SCD: single compartment dosimetry, STD: standard deviation

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 56 patients in the mITT population (28 patients per arm) who received treatment. Of the 56 patients, 10/28 patients (36%) in the MCD arm and 5/28 (18%) in the SCD arm completed the 12-month study. The collection period for AEs in DOSISPHERE was limited to 30 days post treatment, with extension to 3 months for liver events and to the entire trial for treatment-related liver SAEs. The mean study duration was 6.7 months in the MCD treatment arm and 5.8 months in the SCD treatment arm.

Adverse effects:

In the mITT population there were 323 AEs reported among 52 patients (93%), with 93% of patients reporting at least one AE. There were 277 treatment emergent adverse events (TEAEs) reported among 50 patients (89%), with the incidence of patients experiencing at least one TEAE comparable between treatment arms: 93% for MCD and 86% for SCD.

Five patients (9%) had fatal TEAEs during the study: 2 patients (6%) in the MCD arm and 3 patients (14%) in the SCD arm. Two of these fatal TEAEs were considered probably related to study treatment: ascites (in the SCD arm) and hepatic failure (in the MCD arm).

No patients withdrew from the study due to a TEAE.

Table 3 summarizes the most commonly reported related TEAEs (occurring in $\geq 5\%$ of patients in any arm) in the mITT population. Table 4 summarizes all related treatment emergent (TE) serious adverse events (SAEs) by System Organ Class (SOC) and preferred term in the mITT population.

Table 3: Summary of Related TEAEs Occurring in $\geq 5\%$ of Patients (mITT population)

	MCD (N=28)		SCD (N=28)		Total (N=56)	
	All Grades (N=16) n (%)	Grades ≥ 3 (N=12) n (%)	All Grades (N=19) n (%)	Grades ≥ 3 (N=12) n (%)	All Grades (N=35) n (%)	Grades ≥ 3 (N=24) n (%)
Blood and lymphatic system disorders						
Lymphopenia	10 (36)	9 (32)	8 (29)	7 (25)	18 (32)	16 (29)
Thrombocytopenia	1 (4)	0	3 (11)	0	4 (7)	0
Gastrointestinal disorders						
Abdominal pain	2 (7)	0	1 (4)	0	3 (5)	0
Abdominal pain upper	2 (7)	0	1 (4)	0	3 (5)	0
Ascites	2 (7)	1 (4)	5 (18)	1 (3.6)	7 (13)	2 (4)
Nausea	5 (18)	0	2 (7)	0	7 (13)	0
General disorders and administration site conditions						
Asthenia	4 (14)	1 (4)	4 (14)	0	8 (14)	1 (2)
Fatigue	4 (14)	0	2 (7)	1 (4)	6 (11)	1 (2)
Hepatobiliary disorders						
Hepatic failure	2 (7)	1 (4)	1 (4)	1 (4)	3 (5)	2 (4)
Jaundice	0	0	3 (11)	1 (4)	3 (5)	1 (2)
Investigations						
Blood bilirubin increased	2 (7)	1 (4)	2 (7)	0	4 (7)	1 (2)
Lymphocyte count decreased	3 (11)	1 (4)	4 (14)	3 (11)	7 (13)	4 (7)
Metabolism and nutrition disorders						
Decreased appetite	3 (11)	0	1 (4)	0	4 (7)	0

Abbreviations: MCD: multicompartiment dosimetry; mITT: modified intent-to-treat; n: number of patients with TEAE; SCD: single compartment dosimetry; TEAE: treatment-emergent adverse event

Table 4: Summary of all Related Treatment-Emergent SAEs by system organ class and preferred term (mITT population)

MedDRA SOC or Preferred Term	MCD (N = 28)		SCD (N = 28)		Overall (N = 56)	
	n (%)	nAE	n (%)	nAE	n (%)	nAE
Number of patients with at least one related treatment-emergent SAE	2 (7)	3	5 (18)	5	7 (13)	8
GI disorders (Ascites, GI hemorrhage)	1 (4)	1	2 (7)	2	3 (5)	3
General physical health deterioration	0	0	1 (4)	1	1 (2)	1
Hepatobiliary disorders Hepatic failure/necrosis/hyperbilirubinemia	2 (7)	2	2 (7)	2	4 (7)	4

Abbreviations: MCD: multicompartment dosimetry; mITT: modified intent-to-treat; n: number of patients with AE; nAE: number of AE occurrences; SCD: single compartment dosimetry; SOC: system organ class; TEAE: treatment-emergent adverse event

The most commonly reported liver TEAEs overall by subjects were: hyperbilirubinemia (8 patients (29%) in the MCD arm vs 9 patients (32%) in the SCD arm); cytolysis (AST increased, ALT increased, and hepatocellular injury) (7 patients (25%) in the MCD arm vs 3 patients (11%) in the SCD arm); and ascites (3 patients (11%) in the MCD arm and 8 patients (29%) in the SCD arm).

The results presented in Tables 3 and 4 above differ from the results of Garin, et al., 2021 due to reanalysis. In the investigator's analysis, the safety population was defined as the "mITT received" treatment population, where subjects in each randomized arm were re-assigned to "personalized MCD" and "standard SCD" after central dosimetry review. In the reanalysis, AEs were analyzed and compared according to the mITT planned population to allow summaries to be presented by original treatment assignment at randomization. Sensitivity analyses were also performed to align with the data available from the study.

2. Effectiveness Results

The analysis of effectiveness was based on the investigator-assessed OR at 3 months (using EASL) in the mITT population which was the primary endpoint of the study. Of the 56 patients comprising this population, 25 (89%) patients in the MCD arm and 23 patients (82%) in the SCD arm had primary endpoint data. The results met the prespecified stopping criteria and the study was interrupted for efficacy. Sensitivity analyses confirmed the results of the main analysis, with a higher objective response rate (ORR) of the index lesion in the personalized dosimetry group as compared with the standard dosimetry group for all analyses. The primary endpoint of ORR by investigator at Month 3 according to EASL criteria in the treated population was 71% (20/28 patients) and 36% (10/28 patients) in the MCD and SCD arms, respectively (P=0.0074).

Dosimetry and Relation to Efficacy in the DOSISPHERE Study:

Perfused liver absorbed dose, TAD, and normal tissue absorbed dose (NTAD) for pretreatment assessments, by investigator, were significantly higher ($p < 0.05$) in the MCD arm compared with the SCD arm (Table 5). To achieve the target TAD, the MCD arm had an approximate 50% increase in the administered activity of TheraSphere compared to the SCD arm (mean 3.98 (2.02) GBq for the MCD arm and 2.72 (0.93) GBq for the SCD arm). The higher perfused liver absorbed dose and TAD by investigator assessment in the MCD arm resulted in a higher ORR of the index lesion at Month 3 when evaluated by investigator using EASL criteria. Results were confirmed by centralized evaluation.

Table 5: ^{99m}Tc -MAA Pretreatment Dosimetry by CEM Investigator (mITT Population)

	MCD (N = 28)	SCD (N = 28)	p-value^a
Perfused liver absorbed dose (Gy)			
n	28	28	
Mean $\pm$ SD	178.43 $\pm$ 59.93	120.26 $\pm$ 15.24	<0.0001
Median	170.00	120.00	
Min, Max	100.0, 375.0	70.0, 150.0	
≥ 150 Gy	19 (67.9%)	1 (3.6%)	<0.0001
TAD (Gy)^b			
n	24	24	
Mean $\pm$ SD	342.58 $\pm$ 131.45	221.32 $\pm$ 139.42	0.0033
Median	328.50	163.50	
Min, Max	120.0, 704.0	115.0, 707.0	
≥ 205 Gy	21 (87.5%)	9 (37.5%)	0.0008
Normal perfused liver absorbed dose (Gy)^b			
n	23	23	
Mean $\pm$ SD	94.71 $\pm$ 30.25	64.46 $\pm$ 36.64	0.0038
Median	106.00	70.00	
Min, Max	20.0, 140.0	0.0, 133.0	
Absorbed dose in the lungs (Gy)			
n	28	28	
Mean $\pm$ SD	6.92 $\pm$ 9.25	6.25 $\pm$ 9.78	0.7922
Median	1.75	1.20	
Min, Max	0.0, 30.0	0.0, 29.0	

CEM: Centre Eugène Marquis; MCD: multicompartiment dosimetry; mITT: modified intent-to-treat; n: number; SCD: single compartment dosimetry; SD: standard deviation

^a Treatment comparison by exact t-test for means, and by Chi-square test for frequencies.

^b TAD and NTAD were not evaluable for 8 patients due to these patients receiving 2 ^{99m}Tc-MAA injections on the same day.

Note: All percentages were calculated based on number of patients with available data.

Radiation Dosimetry Planning Precision:

Y-90 SPECT/CT or Y-90 PET/CT (N=43) imaging was acquired in DOSISPHERE patients for exploratory analysis of differences between planning- and treatment-day records of administered radioactivity (GBq) and HCC index tumor absorbed dose (Gy). Planning day here refers to the day of ^{99m}Tc-MAA administration. The results of this analysis are shown in Table 6.

Table 6: Radiation Dosimetry Planning Precision

Study patients in whom measured ^a delivery was equal to the planned amount $\pm 20\%$:	Numerator/Denominator = Percentage (%) (95% confidence interval)	
	MCD Arm	SCD Arm
Administered activity (GBq)	22/28 ^b = 79 (59,92)	24/28 ^b = 86 (67,96)
Tumor absorbed dose (Gy)	5/22 ^b = 23 (8,45)	6/21 ^b = 29 (11,52)

^a Measurement based on central review unblinded to investigator-recorded planning information.

^b Of the 56 (28+28) subjects who received a first Y90 treatment (58 vials), 43 (22+21) received post-Y90 imaging, including 3 who had multiple investigator-recorded tumor target dosing plans. A subject was counted for the percentages shown if the measured delivery corresponding to each vial and target was equal to the planned activity (GBq) and tumor dose (Gy) $\pm 20\%$; missing data was imputed conservatively.

Overall survival (OS) and Progression-free survival (PFS):

Analyses of OS and PFS in the ITT population are provided in Table 7. Median OS in the MCD arm was statistically longer versus in the SCD arm.

Table 7: Analyses of OS and PFS According to EASL Criteria in the ITT population, (Garin et al, 2021 & 2024)

Population	MCD Arm N=31	SCD Arm N=29	HR (95% CI) p-value
Garin E et al, Lancet Gastroenterol Hepatol. 2021 Jan;6(1):17-29. Median Follow-up of 27.2 months (IQR – 33.9–18.7).			
OS, median, months (95% CI)	26.6 (11.7–NR)	10.7 (6.0–16.8)	0.42 (0.21–0.83) p=0.0096
Subgroup of patients with PVT, months (95% CI)	22.9 (9.1–NR)	9.5 (5.3–17.6)	0.39 (0.17–0.90) p=0.023
Progression, event (%)	17 (54.8%)	17 (58.6%)	
PFS, median, months (95% CI)	6.0 (3.5–11.6)	3.4 (2.9–8.5)	0.71 (0.39–1.30) p=0.26
Garin E et al, J Nucl Med. 2024 Feb 1;65(2):264-269. Median follow-up was 65.8 months (range, 2.1–73.1 months).			
OS, median, months (95% CI)	24.8 (11–36.5)	10.7 (6–14.9)	0.51 (0.29–0.9) p=0.020
Subgroup of patients with PVT, months (95% CI)	22 (10.3–36.5)	9.4 (5.3–17.6)	0.52 (0.26–0.1) p=0.058

Abbreviations: CI confidence interval; EASL: European Association for the Study of the Liver; HR: Hazard Ratio; ITT: intent-to-treat; MCD: multicompartiment dosimetry; NR: not reached; PVT: portal vein thrombosis, PFS: progression free survival; SCD: single compartment dosimetry

Resection after TheraSphere treatment:

In the mITT population, 18 patients (64%) in the MCD arm and 21 patients (75%) in the SCD arm had PVT at baseline. Resection after SIRT was performed in a statistically significantly higher proportion of patients in the MCD arm (10 (36%)), as compared with the SCD arm (1 (4%)) (p=0.0025).

3. Subgroup Analyses

No subgroup analyses were performed for any relevant patient characteristics.

4. Pediatric Extrapolation

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

TARGET Study

A. Study Design

The TARGET study was leveraged in support of the primary DOSISPHERE study.

TARGET was a retrospective, multinational, single arm study using Simplicit90Y dosimetry software to evaluate MCD in adult patients with HCC who received TheraSphere according to local standard of care.

The primary objective was to explore the relationship between NTAD and safety outcomes and the relationship between TAD and efficacy outcomes. Patients were selected in reverse chronological order to minimize selection bias, based on the date of TheraSphere treatment, between January 1, 2010, and December 31, 2017.

The TARGET study had a projected sample size between 200 and 300 patients which was based on simulated logistic regression curves to assess the primary endpoint. The main analysis population was comprised of all patients enrolled in the study who satisfied eligibility, and the endpoint analyses were performed on this population.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the TARGET study was limited to patients who met the following inclusion criteria (assessed at time of first TheraSphere treatment, unless another or additional time is specifically noted):

- Up to 10 well defined unilobar/bilobar HCC tumor(s) per lobe with at least one tumor ≥ 3 cm $\pm$ PVT
- Liver dominant disease (limited extra-hepatic metastases in the lung and/or lymph nodes are permitted (up to 5 lesions in the lung, with each individual lesion ≤ 2 cm; any number of lymph node lesions with each individual lesion ≤ 2 cm)
- Child-Pugh stage A or B7
- BCLC A, B or C
- Must be male or female, 18 years of age or older
- Bilirubin ≤ 2 mg/dL
- Tumor replacement $< 50\%$ of total liver volume assessed by diagnostic imaging consisting of multi-phase contrast enhanced CT or contrast enhanced MRI
- Diagnostic imaging consisting of multi-phase contrast enhanced CT or contrast enhanced MRI within 3 months prior to TheraSphere administration
- Infusion of ^{99m}Tc -MAA in a single arterial location sufficient to cover up to 10 well-defined tumors per lobe ≤ 6 weeks prior to TheraSphere administration
- Patients must have received TheraSphere in a single treatment setting in one or more arterial locations sufficient to cover up to 10 well-defined tumors

based on angiography. Subsequent TheraSphere treatment to the second lobe may occur at least 4 weeks following the initial TheraSphere treatment

- For patients receiving a second TheraSphere treatment bilirubin levels must have been recorded prior to the second treatment
- Patients must have had clinical evaluation (assessment of liver specific AEs) and laboratory evaluation (at least a serum bilirubin level) at baseline
- Tumor(s), ≥ 3 cm, measurable by mRECIST and RECIST 1.1 at baseline

Patients were not permitted to enroll in the TARGET study if they met any of the following exclusion criteria (assessed at time of first TheraSphere treatment, unless another or additional time is specifically noted):

- Prior external beam radiation treatment to the liver.
- Prior loco-regional liver directed therapy (cTACE, DEB-TACE and SIR-Spheres)
- Prior liver transplantation
- Whole liver TheraSphere treatment following prior liver resection
- TheraSphere administration to ≤ 2 segments (e.g. radiation segmentectomy)
- Additional active therapy (TACE and treatment with SIR-Spheres) between first TheraSphere treatment and 3 month (90 days) imaging
- Hepatic vein invasion
- Diagnosis of disease progression at peri-procedural imaging as compared to the baseline diagnostic imaging (physician's discretion)

2. Follow-Up Schedule

This was a retrospective study. After TheraSphere administration, patients were followed according to site clinical practice, representing real world clinical data.

Patient data were collected through retrospective review and included baseline demographics (age, sex, race), medical history, cancer history disease characteristics Child-Pugh score, BCLC stage and ECOG status; treatment specific variables, including those for the preparation, administration, and imaging of ^{99m}Tc -MAA and Y-90 with a minimum requirement for angiography, to document catheter position; related AEs; and CT or MRI diagnostic contrast enhanced imaging.

Clinical data were collected, as available, at baseline, 3 months, and 6 months. Laboratory testing results (biochemistry, coagulation, hematology, and tumor markers) were collected at baseline, 42 days, and 3 months, and related AEs were collected for up to 3 months. Tumor response was evaluated based on imaging available between 25- and 400-days post-treatment according to mRECIST and RECIST 1.1.

Data on AEs and SAEs occurring within 90 days after the first TheraSphere administration, determined by the investigator to be device-related (or potentially related) to TheraSphere were assessed.

3. Clinical Endpoints

With regard to safety, the relationship between the perfused NTAD and the occurrence of related Grade ≥ 3 hyperbilirubinemia in the absence of disease progression was assessed.

With regards to effectiveness, TheraSphere was evaluated via assessments of ORR at 3 and 6 months (if available) and for all scans up to 400 days from TheraSphere administration by mRECIST and RECIST 1.1 and the assessment of total perfused TAD on OS.

With regard to success/failure criteria, the primary endpoint for the clinical evaluation was determining the mean NTAD, using preprocedural ^{99m}Tc -MAA SPECT or SPECT/CT imaging, corresponding to a $\leq 15\%$ probability of occurrence of $\geq$ grade 3 hyperbilirubinemia (defined as bilirubin 3 times upper limit of normal [ULN] or >3 times baseline value if baseline was abnormal per CTCAE v4.02) in the absence of disease progression. This was performed using pre-procedural ^{99m}Tc -MAA SPECT or SPECT/CT imaging. Per protocol, ^{99m}Tc macroaggregated human serum albumin (^{99m}Tc -HSA) could be used instead of ^{99m}Tc -MAA for SPECT/CT. (^{99m}Tc -HSA may have been used instead of ^{99m}Tc -MAA for either SPECT or SPECT/CT.) The primary endpoint was assessed using logistic regression.

The following statistical analyses were performed for the secondary endpoints: determining the relationship between predicted TAD and ORR (logistic regression), OS (Kaplan-Meier curves), the relationship between TAD and OS (Cox regression) and the relationship between tumor marker AFP response and TAD (logistic regression).

In the safety analyses, AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Hyperbilirubinemia, ascites, pain, fatigue (including asthenia), nausea, and post-embolization syndrome were identified as adverse events of special interest (AESIs). The safety analysis was limited to related AEs with onset within 90 days of TheraSphere treatment.

B. Accountability of PMA Cohort

At the time of database lock, all (100% [209]) patients enrolled in the study were available for analysis at the completion of the study. Table 8 describes patient disposition.

**Table 8: Summary of Patient Disposition:
Part 3 Main Analysis Population (TARGET Study)**

	N=209
Part 3 Main Analysis Population, n	209
Follow-up Duration (days after TheraSphere treatment)	
n	209
Mean (standard deviation)	516.1 (446.04)
Median	398.0
Min, Max	17, 2939
Patients with data at the following analysis visits, n (%)	
42 Days	153 (73.2)
90 Days	156 (74.6)
180 Days	83 (39.7)
Patients without data at any of the above analysis visits, n (%)	4 (1.9)
Patients with data outside of the above analysis visits, n (%)	122 (58.4)
Survival Status^a, n (%)	
Alive	104 (49.8)
Dead	105 (50.2)

^a Survival status was recorded up to the date of each site's Institutional Review Board or Ethics Committee approval for Protocol Versions 4.0 or 4.1.

Note: Follow-up duration is derived based on all available dates, including last date known alive or date of death. Note: A patient is counted as having data at an analysis visit if data is recorded in any of the following eCRF pages: ECOG-PS, Hematology, Biochemistry and Tumor Marker, Coagulation, Child-Pugh Classification, Imaging Follow-up of Baseline Tumor and New Lesions Summary.

Note: Percentages are based on the number of patients in the Part 3 Main Analysis Population.

C. Study Population Demographics and Baseline Parameters

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

A total of 209 patients were enrolled at 13 sites in 8 countries. Relevant baseline patient characteristics are summarized in Table 9 below.

Table 9: TARGET study population baseline characteristics

Baseline Characteristics	TARGET Population N = 209 n (%)
Median age, years (range)	66 (27-87)
BCLC A/B/C	27 (12.9) / 68 (32.5) / 114 (54.5)
Child-Pugh A (5-6)	187 (89.5)
ALBI grade 1/2	80 (38.3) / 123 (58.9)
Portal vein invasion	69 (33.0)
HCC Solitary / Multifocal	145 (69.4) / 64 (30.6)
Target lesion longest diameter, by mRECIST	
<5 cm	51 (24.4)
≥5 to <8 cm	75 (35.9)
≥8 cm	77 (36.8)
Baseline bilirubin	
<1.0 mg/dL	142 (67.9)
≥1 mg/dL	67 (32.1)
Baseline AFP (N = 187)	
≥200 ng/mL	71 (34.0)
≥400 ng/mL	60 (28.7)

The median follow-up duration after TheraSphere treatment was 398 days and ranged from 17 days to about 8 years.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the safety data collection of the 209 patients in the Main Analysis Population available for the evaluation of related AEs within 90 days after the first TheraSphere administration. AEs occurring after 90 days may not have been detected.

For the primary endpoint of Normal Tissue Complication Probability (NTCP) of occurrence of Grade ≥ 3 hyperbilirubinemia in the absence of disease progression curve, the study did not demonstrate a relationship between NTAD and the occurrence of Grade ≥ 3 hyperbilirubinemia in the absence of disease progression (with or without multiple imputation). This was likely due to the small number of patients (n=10) experiencing this AE.

The corresponding NTCP curves using anatomic segmentation did not show evidence of a relationship between absorbed dose to perfused normal tissue or to

whole liver normal tissue and the occurrence of a dose-related AE of interest. TheraSphere were well tolerated in the NTAD range studied, with similar rates of dose related AEs by quartile of NTAD when computed by anatomic segmentation.

Adverse effects:

The key safety outcomes for this study are presented below in Table 10 and Table 11

Table 10 provides an overall summary of related AEs. No related AEs that occurred within 90 days post-treatment led to death. One patient (0.5%) died due to a related AE of hepatic failure; this death occurred 132 days after the initial TheraSphere administration and was due to a later worsening of the event.

Of these 324 related AEs reported in Table 9, 52.5% resolved during the safety collection period of within 90 days after the first TheraSphere administration. There were 123 AEs (38.0%) ongoing at the end of the safety data collection period, and 46 (37%) of these were Grade ≥ 3 . The outcome of 41 AEs (9.6%) was not known at the end of the safety collection period, and 11 of the 31 AEs (35%) were Grade ≥ 3 .

As show in Table 10, a total of 31 related SAEs occurred among 13 patients (6.2%). Eight patients (3.8%) experienced at least one grade 3 SAE and 5 patients (2.4%) experienced at least one grade 4 SAE. Grade 3 SAEs experienced by more than 1 patient per preferred term included ascites and blood bilirubin increased (4 patients each, 1.9%), blood albumin decreased (3 patients, 1.4%), and peripheral edema (2 patients, 1.0%). No grade 4 SAEs were experienced by more than 1 patient per preferred term. Three grade 4 SAEs were considered life-threatening: peritonitis, sepsis, and blood albumin decreased.

Table 11 provides a summary of frequently reported related AEs by preferred term. The incidence rate for the same preferred terms for related non-serious AEs were comparable.

Treatment with TheraSphere under the TARGET study identified no new safety concerns. The type and severity of related AEs observed were consistent with the known safety profile of TheraSphere. There were no unanticipated safety signals, and AEs occurred at expected rates.

**Table 10: Overall Summary of Related Adverse Events:
Part 3 Main Analysis Population**

	Patients (N=209) n (%)	Events n
Related AEs	131 (62.7)	324
Related SAEs	13 (6.2)	31
Related non-serious AEs	130 (62.2)	293
Related AEs of Grade ≥ 3	43 (20.6)	77
Grade ≥ 3 hyperbilirubinemia	10 (4.8)	11
Grade 3	10 (4.8)	10
Grade 4	1 (0.5)	1
Grade 5	0	0
Deaths due to an AE	1 (0.5)	1

AE = adverse event; SAE = serious AE

Note: Percentages are based on the number of patients in the Part 3 Main Analysis Population. The “Part 3 Main Analysis Population” comprised all patients enrolled in the study who satisfied the eligibility criteria.

Note: Only related AEs (ie, AEs with relationship of Possibly Related, Probably Related or Related to study treatment) and AEs with unknown relationship to study treatment, are included in this table.

Note: Patients who experience multiple AEs are only counted once at the greatest severity.

Note: AEs of hyperbilirubinemia include preferred terms of 'Hyperbilirubinemia', 'Blood bilirubin increased', and 'Hepatic failure'.

**Table 11: Related Adverse Events Reported by $\geq 5\%$ of Patients
in TARGET by Severity Grade**

Preferred Term	All Grades N=209 n (%)	Grades 3-4 N=209 n (%)
Ascites	38 (18.2)	10 (4.8)
Fatigue	34 (16.3)	1 (0.5)
Elevated bilirubin (blood bilirubin increased, hyperbilirubinemia)	29 (13.9)	9 (4.3)
Abdominal pain	26 (12.4)	2 (1.0)
Lymphocyte count decreased	25 (12.0)	16 (7.6)
Asthenia	19 (9.1)	1 (0.5)
Decreased appetite	13 (6.2)	1 (0.5)
Nausea	11 (5.3)	0

a. Effectiveness Results

The analysis of effectiveness was based on the 209 evaluable patients in the Main Analysis Population across the collection period. Key effectiveness outcomes are presented below.

An analysis of all-lesions, according to RECIST 1.1, showed an ORR of 34.4% and an ORR of 38.8% for the target lesion. According to mRECIST, based on all lesions an ORR of 61.7% was observed, and an ORR of 70.8% was observed for the target lesion.

ORR, based on all lesions, by subgroups of total perfused TAD by anatomic segmentation, by RECIST 1.1 and mRECIST are shown in Table 12.

Logistic regression demonstrated that increasing total perfused TAD was associated with higher ORR for both mRECIST and RECIST 1.1 measurements ($p=0.044$ and $p=0.030$, respectively) for anatomic segmentation.

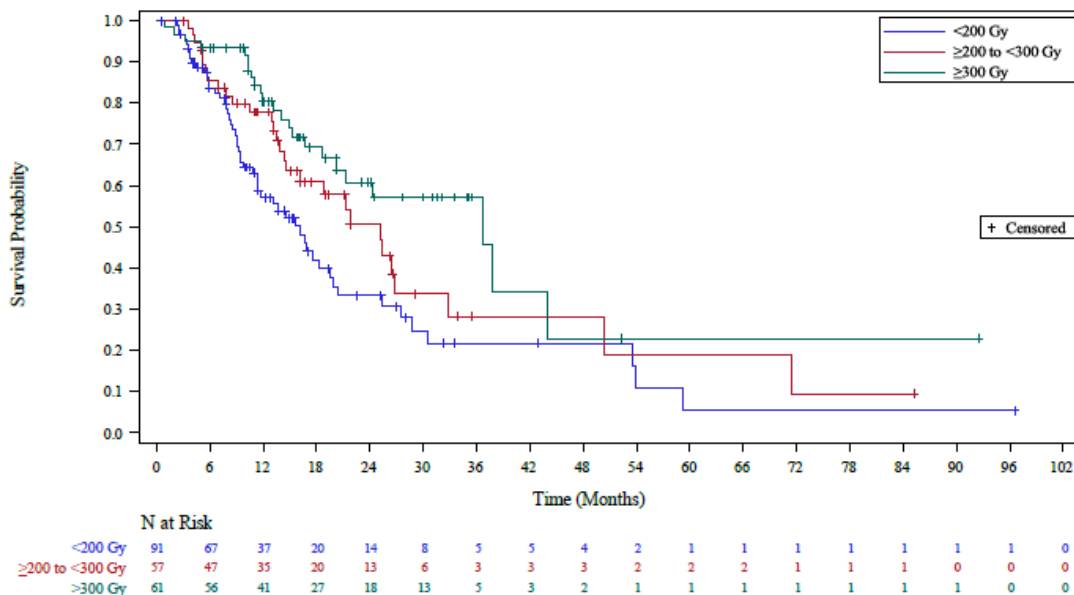
Table 12: Objective Response Rate on all lesions by RECIST 1.1 and mRECIST by Subgroups of Total Perfused TAD by Anatomic Segmentation: Main Analysis Population

Subgroup	RECIST 1.1	mRECIST
<200 Gy, n= 91	26.4%	52.7%
≥ 200 to <300 Gy, n= 57	33.3%	64.9%
≥ 300 Gy, n= 61	47.5%	72.1%

The total perfused TAD had a statistically significant association with OS ($p=0.009$) with a hazard ratio of 0.826 (95% CI: 0.714, 0.954), corresponding to each 100 Gy increase in TAD. Separate analyses of OS were performed in the following subgroups, showing the impact of TAD on median OS (Figure 1):

- <200 Gy: 16.1 months
- ≥ 200 to <300 Gy: 25.1 months
- ≥ 300 Gy: 36.7 months

Figure 1. Kaplan-Meier Curves for OS by Subgroups of Total Perfused TAD by Anatomic Segmentation: Main Analysis Population



b. Pediatric Extrapolation

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

XI. 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. Two pivotal studies are included with this submission. DOSISPHERE, an investigator-sponsored clinical study, included 42 investigators, none of which were full-time or part-time employees of the Applicant. The Applicant acted with due diligence to obtain from the investigator-sponsor the required information. Financial interests/arrangements were not collected, as they were not required under French regulations. The Applicant is not aware of any disclosable financial interests from the DOSISPHERE study investigators. The sponsored-led TARGET study included 50 investigators, of which none were full-time or part-time employees of the sponsor and 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.

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 because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the DOSISPHERE study, the analysis of effectiveness in the mITT population, based on the index lesion ORR at 3 months (according to EASL criteria and investigator assessment), showed a statistically significant difference between arms: 71% in the MCD arm and 36% in the SCD arm ($p=0.0074$). The results met the prespecified stopping criteria and the study was interrupted for efficacy. In the TARGET study, a correlation between TAD and ORR was found using both mRECIST and RECIST 1.1 criteria. OS was longer with increased TAD.

B. Safety Conclusions

The risks of the device are based on data collected in the DOSISPHERE and TARGET clinical studies conducted to support PMA supplement approval as described above as well as from data collected over 23 years of commercial and clinical use in the treatment of liver cancer in >70,000 patients globally. In the DOSISPHERE study events were equally distributed among treatment arms and differences were not statistically significant. The most frequently reported TEAEs were lymphopenia, pain and nausea. No patients withdrew from the study due to a TEAE. When severe (Grade ≥ 3) or serious, the TEAEs reported for both treatment arms were either lymphopenia or liver related events (ascites, AST/ALT increase, hyperbilirubinemia, hepatic failure, GI bleeding). In total, 27% of patients reported treatment-emergent SAEs; more patients (36%) in the SCD arm experienced SAEs than in the MCD arm (18%). Among the 8 related treatment-emergent SAEs, ascites ($n=2$) and hepatic failure ($n=2$) were the most frequently reported, with no difference between the 2 treatment arms. Five patients (9%) had fatal TEAEs during the study: 2 patients (7%) in the MCD arm and 3 patients (11%) in the SCD arm. Two of these fatal TEAEs were considered probably related to study treatment: ascites (in the SCD arm) and hepatic failure (in the MCD arm).

In the TARGET study, 62.7% of patients had a total of 324 related events (AEs and SAEs). Most related AEs were mild or moderate events, and the most common reported

events were ascites, fatigue/asthenia, abdominal pain, hyperbilirubinemia/blood bilirubin increased, lymphocyte count decreased, decreased appetite, and nausea. Most AEs resolved during the safety data collection period of 90 days after the first TheraSphere administration. No related AEs that occurred within 90 days post-treatment led to death. One patient (0.5%) died due to a related AE of hepatic failure; this death occurred 132 days after the initial TheraSphere administration and was due to a later worsening of this event. An association between NTAD and the probability of occurrence of elevated bilirubin Grade ≥ 3 was not statistically significant.

There were no new safety signals and the AEs that occurred in these studies were consistent with those observed in marketed use of TheraSphere. In both DOSISPHERE and TARGET, TheraSphere were well tolerated in the NTAD range studied.

Principal limitations with both studies were limited long-term AE monitoring and follow-up.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in two clinical studies conducted to support PMA supplement approval as described above.

In the DOSISPHERE study, the probable benefits of the labeling expansion are based on the ORR in the index lesion at 3 months (EASL and investigator assessment) being higher in the MCD arm (71%) than in the SCD arm (36%). As a consequence of the ORR improvement, patients were secondarily resected, including 10 of 28 (35.7%) in the MCD arm compared to 1 of 28 (4%) in the SCD arm with the difference in resection rates being attributed to local tumor control, which was attributed to the ORR improvement. Median OS was 24.8 months in the MCD arm compared to 10.7 months in the SCD arm, with a median follow-up of 65.8 months. The results for the primary endpoint met the prespecified stopping criteria and the study was interrupted for efficacy. The percentage of patients with an ORR, the number of patients converted to resection, and the length of OS all were improved in the MCD arm compared to the control arm. The improvement occurred across tumor sizes, with solitary or multifocal disease and in the presence or absence of PVT.

Secondary to the DOSISPHERE study, TARGET provided data to support the labeling expansion. Logistic regression demonstrated that increasing total perfused TAD was associated with higher ORR for both mRECIST and RECIST 1.1 measurements for anatomic segmentation. The total perfused TAD had a statistically significant association with OS.

The probable risks of SIRT with TheraSphere are well established for the HCC patient population, based on 25 years of clinical use in >70,000 patients globally. The probable risks for the labeling expansion are based on data collected in the DOSISPHERE and TARGET studies conducted to support the PMA supplement approval as described above. Regarding DOSISPHERE, the baseline characteristics are representative of

patients who have more extensive disease and are sicker than those indicated in the Indications for Use and the safety profile did not differ between treatment arms. However, a principal limitation is that the collection period for AEs was limited (30 days post treatment, with extension to 3 months for liver events and to the entire trial for treatment-related liver SAEs). The mean study duration in DOSISPHERE was 6.7 months in the MCD arm and 5.8 months in the SCD arm. Regarding TARGET, as a retrospective study, a principal limitation is that it is not certain if all AEs were captured and recorded, and the safety analysis was limited to related AEs with onset from the day of TheraSphere administration through 90 days after TheraSphere treatment.

Factors to be considered in determining probable risks and benefits for TheraSphere include the retrospective nature of the TARGET study, the length of follow-up and AE collection was limited, and the on-label sample size was limited.

In conclusion, given the available information above, and based on the probable benefits outweighing the probable risks, the data support the labeling expansion.

1. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of MCD labeling when used in accordance with the indications for use and with the recommendations in the TheraSphere labeling. Based on the information presented in this assessment, the benefits associated with the use of TheraSphere under this labeling expansion outweigh the risks for the treatment of HCC in the intended patient population.

XIV. CDRH DECISION

CDRH issued an approval order on February 10, 2026. The final clinical conditions of approval cited in the approval order are described below.

The Post Approval Study (PAS) titled *A post approval single-arm study evaluating Transarterial Radioembolization treatment for Hepatocellular Carcinoma using multi-compartment dosimetry planning (MCD-HCC)* is an open label, single arm, prospective, US study to evaluate the safety and effectiveness of TheraSphere administration using multicompartiment dosimetry in patients with unresectable HCC. The primary endpoint will be the Rate of Radioembolization Induced Liver Disease (REILD) grade ≥ 3 up to 4 months after any TheraSphere treatment administration before progression. A total of 140 evaluable patients will be followed for 13-months, which will include adverse event monitoring. Two interim analyses are planned when approximately one-third and one-

half of the target sample size has been enrolled. The interim analyses will be used to determine if the pre-specified stopping criteria are met. However, all evaluable enrolled patients will be followed for 13 months. Information regarding interim study progress and results (including number of study sites and patients enrolled, as well as a summary of anticipated and unanticipated adverse events) will be posted on the FDA's Post-Approval Studies (PAS) database webpage after submission of each report.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

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

Garin, E., Tselikas, L., Guiu, B. et al, 2021. Personalized versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomized, multicentre, open-label phase 2 trial. *Lancet Gastro Hepat*, Volume 6, pp. 17-29.

Garin, E., Tselikas, L., Guiu, B. et al, 2024. Long-Term overall survival after selective internal radiation therapy for locally advanced hepatocellular carcinomas: Updated analysis of DOSISPHERE-01 trial. *J Nucl Med*, Volume 65, pp. 264-269.