SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Microspheres Radionuclide

Device Trade Name: SIR-Spheres® Y-90 Resin Microspheres

Device Procode: NAW

Applicant's Name and Address: Sirtex Medical Pty Ltd
Shop 6, 207 Pacific Highway
St. Leonards, New South Wales 2065, Australia

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P990065/S014

Date of FDA Notice of Approval: 07/01/2025

The original PMA (PMA P990065) was approved on March 05, 2002 (Radiological Devices Advisory Panel recommendation on November 6, 2000) and indicated for the treatment of unresectable metastatic liver tumor from primary colorectal cancer with adjuvant intrahepatic artery chemotherapy (IHAC) of FUDR (Floxuridine). The SSED to support that indication is available on the CDRH website and is incorporated by reference here. This supplement is being submitted to expand the indication for the SIR-Spheres® Y-90 Resin Microspheres (SIR-Spheres) device.

II. INDICATIONS FOR USE

SIR-Spheres® Y-90 resin microspheres are indicated for the local tumor control of unresectable hepatocellular carcinoma (HCC) in patients with no macrovascular invasion, Child Pugh-A cirrhosis, well-compensated liver function, and good performance status. They are also indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intrahepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

III. CONTRAINDICATIONS

All Patients: SIR-Spheres® Y-90 resin microspheres are contraindicated in any patient who has:

- portal vein thrombosis;
- ascites or clinical liver failure;
- markedly abnormal synthetic and excretory liver function tests (LFTs), such as total bilirubin > 2.0 mg/dL or albumin < 3.0 g/dL;

- 20% lung shunting of the hepatic artery blood flow, or > 30 Gy radiation absorbed dose to the lungs for a single treatment, or > 50 Gy cumulative radiation absorbed dose to the lungs if the patient is re-treated, as estimated by the ^{99m}Tc-MAA scan;
- Pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of microspheres to the stomach, pancreas or bowel;
- had previous external beam radiation therapy to the liver.

Patients with mCRC:
- disseminated extra-hepatic malignant disease;
- been treated with capecitabine within the two previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres® Y-90 resin microspheres.

Patients with HCC:
- comorbidities or poor overall health (e.g., ECOG performance status rating> 2), which may make the patient a poor candidate for locoregional radiation treatment;
- disseminated extra-hepatic malignant disease.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SIR-Spheres® Y-90 Resin Microspheres labeling.

V. DEVICE DESCRIPTION

SIR-Spheres® Y-90 resin microspheres consist of biocompatible microspheres containing yttrium-90 with a size between 20 and 60 microns in diameter. Yttrium-90 is a high-energy pure beta-emitting isotope with no primary gamma emission. The maximum energy of the beta particles is 2.27 MeV with a mean of 0.93 MeV. The maximum range of emissions in tissue is 11 mm with a mean depth of 2.5 mm. The half-life is 64.1 hours. In therapeutic use, requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days. The number of particles provided in each SIR-Y001 5mL vial for implantation is 40-80 million microspheres, and the number of particles provided in each SIR-Y002 3mL vial for implantation is 24-48 million microspheres. SIR-Spheres® Y-90 resin microspheres are a permanent implant.

SIR-Spheres® Y-90 resin microspheres are implanted into a hepatic tumor by injection into either the common hepatic artery or the right or left hepatic artery or more selectively using a catheter or chemotherapy catheter port. The SIR-Spheres® Y-90 resin microspheres distribute non-uniformly in the liver, primarily due to the unique physiological characteristics of the hepatic arterial flow, the tumor to normal liver ratio of the tissue vascularity, and the size of the tumor. The tumor usually gets higher density per unit distribution of SIR-Spheres® Y-90 resin microspheres than the normal liver. The density of SIR-Spheres® Y-90 resin microspheres in the tumor can be as high as 5 to 6 times of the normal liver tissue. Once SIR-Spheres® Y-90 resin microspheres are

implanted into the liver, they are not metabolized or excreted, and they stay permanently in the liver. Each device is for single patient use.

SIR-Spheres® Y-90 resin microspheres are either supplied with an activity of 3 GBq ±10% at the calibration time and date in ~5 mL of non-pyrogenic water for injection or with an activity of 1.8 GBq ±10% at the calibration time and date in ~3 mL of non-pyrogenic water for injection. Refer to Figure 1 for a photo of SIR-Spheres® Y-90 resin microspheres.

Figure 1. SIR-Spheres® Yttrium-90 Microspheres (SIR-Y001)

A single use delivery set is provided for each dose. Each user site is also provided with a re-usable delivery apparatus that provides both radiation protection for the user and physical support of the dose v-vial and delivery set during administration of the device. The delivery set and delivery apparatus are Class I devices.

SIR-Spheres® Y-90 resin microspheres adds to the clinical armamentarium for hypervascular tumors (e.g., Metastatic Colorectal Cancer/mCRC and HCC). The microspheres have a relatively low density (1.1 g/mL; vs. whole blood, 1.05 mg/mL), allowing them to be preferentially distributed to the tumor, due to the increased blood flow to the tumor, as compared to normal liver parenchyma. The size of the microspheres allows for significant penetration into the neovasculature of the tumors. With a median diameter of 32.5µm they are small enough to become lodged in the arterioles of the tumor, while being too large to enter the venous system via the capillaries.

SIR-Spheres® Y-90 resin microspheres are administered by a trained Interventional Radiologist employing local anesthetic and moderate sedation. As depicted in Figure 2, the radiologist accesses the arterial system through standard percutaneous access via the femoral artery near the groin or radial artery in the wrist (A). A microcatheter is then guided through the artery to the hepatic artery. SIR-Spheres® Y-90 resin microspheres are administered through this microcatheter (B), where microspheres preferentially deposit into the tumor microvasculature (C). SIR-Spheres® Y-90 resin microspheres can be delivered to the entire liver, an individual liver lobe, selectively to a liver segment, or sub-

segment, depending upon the medical decisions, intent for therapy, and based on the pre-procedure planning.

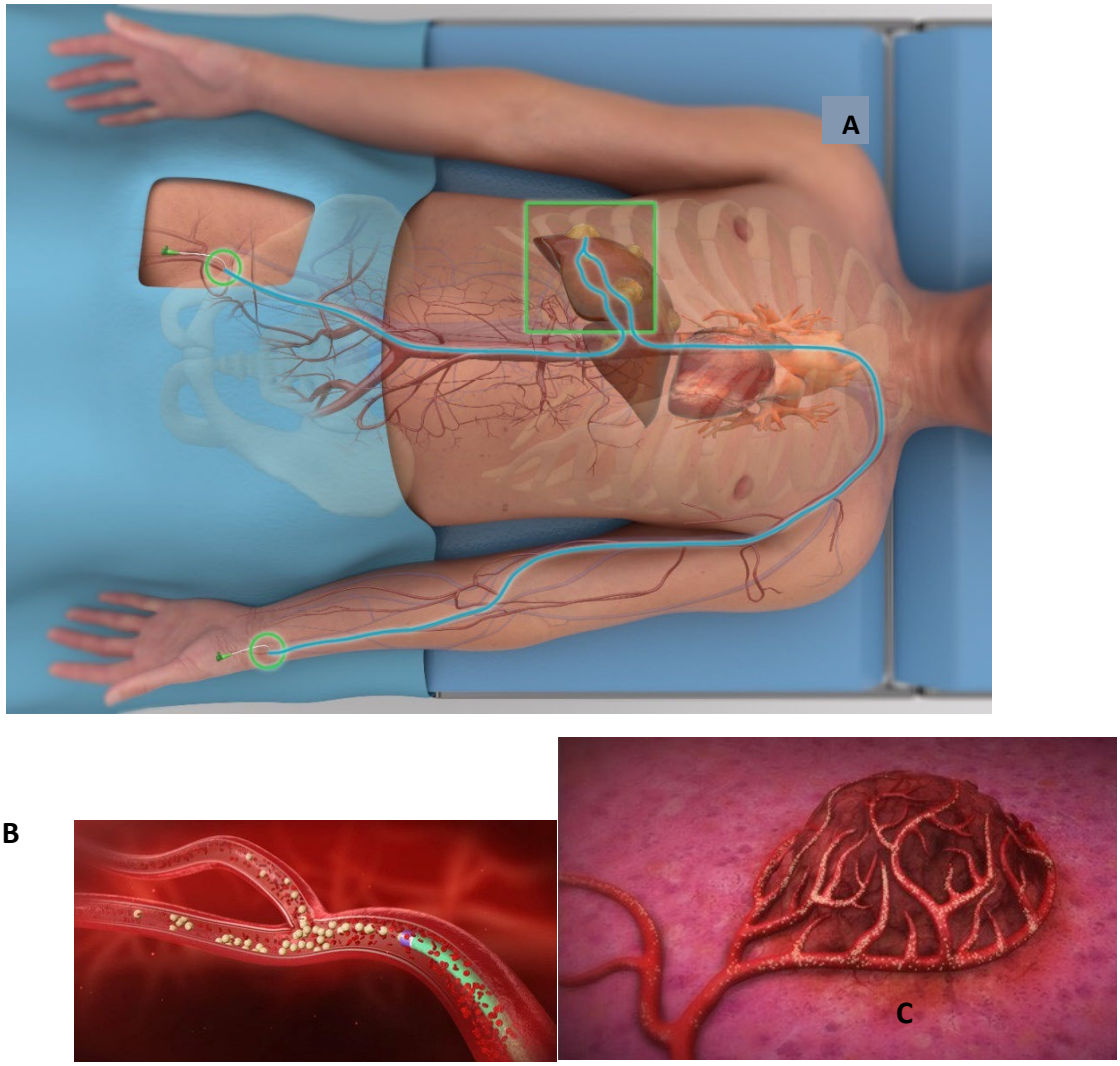

Figure 2. Administration of SIRT using SIR-Spheres® Y-90 resin microspheres. The radiologist accesses the arterial system through standard percutaneous access via the femoral artery near the groin or radial artery in the wrist (A). A microcatheter is then guided through the artery to the hepatic artery. SIR-Spheres® Y-90 resin microspheres are administered through this microcatheter (B), where microspheres preferentially deposit into the tumor microvasculature (C).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are various alternative practices for the treatment of unresectable HCC, dependent on disease stage, treatment intent, and the patient's overall well-being. Liver transplantation and liver resection are considered curative strategies for early-stage HCC because they address the cancer and the underlying liver disease; liver transplantation,

however, is limited by donor organ shortage. Locoregional therapies have a wide range of curative and palliative indications. 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 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

SIR-Spheres® Y-90 resin microspheres are FDA Approved under PMA Approval Number P990065 and have been administered through its Delivery System since initial FDA approval in March 2002. The SIR-Spheres® Y-90 resin microspheres and the Delivery System have been approved globally in Canada (2016), the European Union (2002), the Middle East (2012), Asia (2011), Australia (1998), and Latin America (2012). The device has not been withdrawn from marketing for any reason related to its safety or 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. 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 SIR-Spheres® Y-90 resin microspheres, 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 decompensation
- Dyspnea
- Edema (any location)
- Electrolyte abnormalities
- Elevated BUN/creatinine
- Fall
- Fatigue Disease
- Fever
- Gastrointestinal bleeding/ hemorrhage
- Gastrointestinal ulcer or ulceration

- Hepatic encephalopathy
- Hepatorenal failure edema)
- 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
- Pre-existing chronic liver disease
- Portal hypertension
- Pulmonary edema
- Pulmonary fibrosis
- Radiation hepatitis
- Radiation induced disease, acute
- Radioembolization 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
- Bruising / bleeding / hematoma at site
- Constipation / abdominal distension
- Fatigue
- Flushing
- Infection
- Nausea
- Nerve damage
- Pain (any location)
- Vomiting

For the specific adverse events that occurred in the clinical study, please see Section X.D.1 below.

IX. SUMMARY OF NON-CLINICAL STUDIES

All non-clinical laboratory studies are included as part of the original PMA P990065 and follow-on supplements. Refer to the current SIR-Spheres® Y-90 resin microspheres SSED available on the FDA website.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

A prospective clinical study was performed to establish a reasonable assurance of safety and effectiveness of Selective Internal Radiation Therapy with SIR-Spheres® Y-90 Resin Microspheres for the local tumor control of unresectable hepatocellular carcinoma (HCC) in patients with no macrovascular invasion, Child Pugh-A cirrhosis, well-compensated liver function, and good performance status in the US under IDE# G200352. 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 DOORwaY^{90} study is an ongoing pivotal, prospective, multicenter, open-label, single-arm study evaluating treatment with hepatic arterial injection of SIR-Spheres® Y-90 resin microspheres. The study began enrollment on May 20, 2021, and the final subject was enrolled on Aug 6, 2024. The study was conducted in adult subjects and did not include any age, gender, racial or ethnic origin restrictions. A total of 100 patients were planned.

The database for this Panel Track Supplement reflected data collected for a pre-planned interim analysis and included 100 treated subjects with safety and dosimetry assessments (the *safety* cohort), 65 of whom had tumor response adjudicated by an independent core laboratory (the *effectiveness cohort*). There were 28 U.S. investigational sites.

The DOORwaY^{90} study objective was to evaluate the safety and effectiveness of SIR-Spheres® Y-90 resin microspheres for the treatment of unresectable HCC in the intended study population. Effectiveness was evaluated by overall response rate (ORR) using a localized version of modified Response Evaluation Criteria in Solid Tumors (localized mRECIST) criteria and best response through 9 months of response, and by duration of response (DoR), defined as the interval from first time of response (partial response (PR) or complete response (CR) until disease progression (PD). For subjects with response and no subsequent PD, DoR was calculated as ending at the last imaging assessment. Similarly, subjects with response who later underwent curative treatment had DoR calculated as ending at the last imaging assessment before the curative treatment. Tumor response assessments were adjudicated by an independent core laboratory.

Primary endpoint success was defined as meeting the following two criteria:

- Lower limit of 95% confidence interval (CI) for ORR by localized mRECIST >40% and
- Duration of response (DoR) ≥6 months for ≥60% of responders

For ORR, the condition of 40% in comparison to a confidence interval constituted a hypothesis test; both p-values and confidence intervals were then calculated. For DoR, the threshold referred to the point estimate being at least 60% without the use of

confidence intervals, and this endpoint was therefore presented descriptively. Only subjects demonstrating a response applied toward the DoR endpoint. Given a two-sided test at 0.05 alpha and desired power of 80%, the required evaluable sample size using the exact method for a single proportion and the worst estimate above (55%) is no greater than 90. A study sample size of 100 total subjects therefore provided appropriate powering for hypothesis testing as described above.

To preserve overall Type I error, Lan-DeMets alpha-spending using O'Brien-Fleming boundaries was applied to hypothesis testing as part of the interim analysis. Consequently, a p-value of 0.007 or less was required to reject the null hypothesis for ORR, and ORR outcomes are presented using 99.3% confidence intervals rather than 95% confidence intervals.

The ORR was evaluated by independent central image review using localized mRECIST criteria with best response through 9 months. This was assessed for each enrolled subject in the effectiveness cohort and presented as a proportion of successes with corresponding CIs calculated via the exact binomial (Clopper-Pearson) method.
The study used segmentectomy/partition dosimetry methods (see labeling for the formulas). When planning for a radiation segmentectomy, the recommended radiation absorbed dose to the target liver segment was 150 Gy to 400 Gy. Recommended normal tissue constraints are 30 Gy per treatment and 50 Gy cumulatively to the lungs. When planning to perfuse multiple liver segments separable into a perfused tumor partition and a perfused normal liver partition, the recommended radiation absorbed dose to the target tumor partition was 150 Gy to 400 Gy. Recommended normal tissue constraints are 150 Gy to the perfused normal liver, 30 Gy per treatment, and 50 Gy cumulatively to the lungs.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the DOORwaY^{90} study was limited to patients who met the following inclusion criteria:

   1. Willing, able, and mentally competent to provide written informed consent;
   2. Age 18 or older at the time of consent;
   3. All tumors must be measurable by CT or MRI according to localized mRECIST;
   4. Life expectancy ≥6 months (to allow for adequate completion of study procedures and collection of data);
   5. Diagnosis of HCC with Liver Imaging Reporting and Data System (LI-RADS) 4 or 5 or by histology;
   6. Treatment-naïve patients or patients who have developed a new lesion following one of these prior locoregional treatments:
      a. Liver resection with negative pathologic margins, no microvascular invasion, and no recurrence at resection margins

for at least 6 months post-treatment and no new lesions within 6 months of liver resection;

b. Ablation of a single ≤3 cm lesion with no recurrence of the treated lesion for at least 6 months post-treatment;

7. BCLC (Barcelona Clinic Liver Cancer) stage A, B1, B2, and C with maximal single tumor size of ≤8 cm and sum of the maximal tumor dimensions ≤12 cm with the entire tumor burden expected to be treatable within the perfused volume;
8. At least one lesion ≥1 cm in diameter (long axis) measured according to mRECIST criteria by CT or MRI;
9. Child-Pugh score of A5 or A6 at baseline;
10. Eastern Cooperative Oncology Group (ECOG) performance score of ≤1 at baseline;
11. Adequate blood count, liver enzymes, and renal function at baseline:
    a. Platelet count >50,000/microliter (patients may not receive a platelet transfusion or growth factors to increase the platelet count so that the patient may be eligible for the study).
    b. WBC ≥3 x 10^9/L;
    c. Hemoglobin >8.5 g/dL;
    d. AST & ALT <5x upper limit normal;;
    e. Bilirubin ≤2.0 mg/dL;
    f. Albumin >3.0 g/dL;
    g. International normalized ratio (INR) ≤2.0;
    h. Glomerular filtration rate (GFR) >50.
12. Negative serum pregnancy test at baseline;
13. Life expectancy of >3 months without any active treatment.

Patients were <u>not</u> permitted to enroll in the DOORwaY^{90} study if they met any of the following exclusion criteria:

1. Patients eligible for ablation or resection for their malignancy, in the opinion of the investigator, at the time of screening;
2. Prior systemic anti-cancer therapy (including immunotherapy and/or targeted therapy), radiotherapy or use of other investigational agents for the treatment of HCC;
3. Intrahepatic arteriovenous shunting (arteriovenous shunting resulting from a biopsy is allowed but must be embolized during the pre-treatment mapping procedure);
4. Incompetent biliary duct system, prior biliary intervention or a compromised Ampulla of Vater;

5. Planned localized cancer treatment to the liver, other than the study treatment, throughout the duration of the study;
6. Planned systemic cancer treatment throughout the duration of the study;
7. Patients with portal vein thrombosis;
8. Patients with extrahepatic disease;
9. Patients with contraindications to angiography and selective visceral catheterization;
10. Evidence of extrahepatic collateral supply to the tumor;
11. Evidence of potential delivery of mean radiation dose >30 Gy to the lungs (single treatment);
12. Evidence of any detectable 99mTc-MAA flow outside of the liver in the abdomen, after application of established angiographic techniques to stop or mitigate such flow (e.g., placing catheter distal to gastric vessels or coiling);
13. Evidence that < 33% of the total liver volume is disease-free and will be spared SIR-Spheres treatment;
14. Prior liver resection and/or liver transplant, with exception for patients with prior resection who meet inclusion criterion 6a;
15. Female patients who are pregnant, breastfeeding, or premenopausal and unwilling to use an effective method of contraception through the 1 year follow-up; males unwilling to use effective method of contraception for 30 days post-procedure;
16. Medical history of clotting disorders;
17. Underlying pulmonary disease requiring chronic oxygen therapy;
18. Evidence of portal hypertension with ascites as seen on cross-sectional imaging or any history of prior variceal bleeding within 6 months prior to screening;
19. Concurrently enrolled in another study unless it is an observational, noninterventional study;
20. Active infection (hepatitis B [HBV] infection with ongoing HBV treatment and successfully treated hepatitis C infection are allowed);
21. History of other cancer with current active treatment;
22. Patients with drug or alcohol dependency (within 6 months prior to study entry) in the opinion of the investigator;
23. History of severe allergy or intolerance to contrast agents, narcotics, or sedatives;
24. Any condition that, in the opinion of the investigator, would interfere with safe delivery of the study treatment or with the interpretation of study results.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1, 2, 4, 6, 9, 12 months (± 2 weeks), and 2 years (± 1 month) following the SIRT procedure.

A list of all assessments and data collected at each study timepoint, both preoperatively and postoperatively, is provided in Table 1 below:

Table 1. Assessments and Data Collection at Each Study Timepoint

Evaluations	Screening/ Baseline[1]	Review Committee Approval	SIRT Procedure	SIRT Re-Treatment[2]	Follow-Up Visits Post-Initial SIRT Procedure		
					1 month (±2 weeks)	2, 4, 6, 9, 12 months (±2 weeks)	2 years (±1 month) clinic/phone
Subject informed consent	X						
Inclusion/exclusion assessment	**X**						
Physical exam including vital signs	X					X	
Demographics & medical history	X						
Pregnancy test	X						
Child-Pugh assessment	X			X			
Laboratory tests[3]	X		X	X	X	X	
^{99m}Tc-MAA lung shunt scan and liver SPECT/CT	X						
Imaging (CT or MRI) of chest, abdomen, & pelvis	X					X[4]	
Hepatic angiography	X		X	X			
Treatment plan assessment	X						
ECOG performance test	**X**						
Medication assessment	**X**		**X**	**X**		**X**[5]	
Tumor evaluation (mRECIST)[6]	**X**					**X**	
CB-CT (or in-room fan-beam CT)	X		X	X			
SIR-Spheres treatment			**X**	**X**			
Y-90 SPECT/CT or Y-90 PET/CT Post-treatment imaging			X	X			
Adverse event assessment	**X**		**X**	**X**	**X**	**X**	**X**
Questionnaires (EQ-5D-5L, FACT-Hep)			**X**[7]			**X**	

[1] Performed ≤28 days prior to SIRT procedure.
[2] SIRT re-treatment could occur at the discretion of the treating physician ≤4 weeks of initial SIRT procedure.
[3] CBC/Diff, biochemistry, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin (direct and indirect), albumin, GFR, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR). Hepatitis B and C serology collected only at baseline.
[4] Modality of abdominal imaging (CT or MRI) was required to match method used at baseline.
[5] All concomitant medications collected through 2 months; after 2 months, only oncologic and/or liver specific medications were collected.
[6] Abdominal images sent to core lab for analysis.
[7] Completed pre-procedure.
Note: Study-specific assessments are noted in **bold red**.

3. Clinical Endpoints

With regards to safety, the occurrence of Grade ≥3 toxicities (CTCAE v5.0) at 2 months and 6 months were assessed. The adverse events were adjudicated and classified for diagnosis, severity, seriousness, and device and procedure relatedness

by the Clinical Events Committee (CEC), made up of non-investigator physicians, according to the CEC Adjudication Guidelines.

With regards to effectiveness, the ORR using localized mRECIST criteria, best response through 9 months, and DoR as defined by localized mRECIST criteria were assessed by an independent imaging core lab.

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 95% CI for ORR by localized mRECIST >40% and
- DoR ≥6 months for ≥60% of responders

This endpoint was assessed for each enrolled subject in the effectiveness cohort and presented as a proportion of successes with corresponding CIs calculated via the exact binomial (Clopper-Pearson) method. As an interim analysis was conducted, to preserve overall Type I error, an alpha-spending function was applied to the analysis of the co-primary endpoints using O'Brien-Fleming boundaries. Based on the number of subjects in the effectiveness cohort (that is, those contributing to the ORR primary endpoint), the formal hypothesis test of ORR was conducted at an alpha level of 0.007.

Intra-hepatic Technetium MAA Radiation Absorbed Doses

A sub-study was conducted to evaluate the dosimetry of ^{99m}Tc-MAA after intra-arterial administration to the whole body and non-liver critical organs. The investigation was a prospective, single center, open label, single-arm study. The intended population for the study was patients who were undergoing evaluation for SIR-Spheres® Y-90 resin microspheres administration. Patients enrolled in the study had 3 imaging scans taken after ^{99m}Tc-MAA injection, the final of which occurred between 18 and 24 hours postinjection.

B. Accountability of PMA Cohort

At the time of the interim analysis, of the 100 patients enrolled in the PMA study, 100 patients (100%) patients had safety and dosimetry assessments (the safety cohort), 65 of whom had imaging for tumor response adjudicated by the independent core laboratory (the effectiveness cohort). At the time of the interim analysis, 160 subjects consented, 54 subjects failed screening, 17 subjects had completed the study, 30 subjects had exited early (primarily due to 12 liver transplants and 13 deaths, none of which are related to the device or procedure), and 53 were continuing with follow-up.

C. Study Population Demographics and Baseline Parameters

The demographics of the HCC study population is as follows:

Subject baseline demographics and medical history are presented in Table 2. The mean subject age was 68.4 ± 10 years (range 33 to 91 years) and 75% were male. The most common pre-existing liver disease conditions were cirrhosis (48%) and Non-Alcoholic Steatohepatitis (NASH) or Non-Alcoholic Fatty Liver Disease (NAFLD; 22%). At

baseline, 80% of subjects had early HCC (BCLC Stage A), and all subjects were Child-Pugh A. Tumor size ranged from 3.0 to 80.0 mm (median 27.0 mm).

Table 2. Study Population Demographics and Baseline Data

Characteristic	**N=100**
Age (years) at enrollment	
N	100
Mean ± SD	68.4 ± 10.0
Median (range)	69.0 (33.0-91.0)
Sex, % (n/N)	
Male	75.0% (75/100)
Female	25.0% (25/100)
Race, % (n/N)	
White	69.0% (69/100)
Asian	10.0% (10/100)
Black or African American	7.0% (7/100)
Other	7.0% (7/100)
Subject chose not to disclose race	7.0% (7/100)
American Indian or Alaska Native	0.0% (0/100)
Native Hawaiian or Other Pacific Islander	0.0% (0/100)
Ethnicity, % (n/N)	
Not Hispanic/Latinx	81.0% (81/100)
Hispanic/Latinx	14.0% (14/100)
Subject chose not to disclose	5.0% (5/100)
Medical History	
ECOG performance score, % (n/N)	
0	80.0% (80/100)
1	20.0% (20/100)
Child-Pugh, % (n/N)	
A5	79.0% (79/100)
A6	21.0% (21/100)
BCLC Stage, % (n/N)	
A	80.0% (80/100)
B1	15.0% (15/100)
B2	2.0% (2/100)
C	3.0% (3/100)
Pre-existing liver disease,[1] % (n/N)	92.0% (92/100)
Cirrhosis	48.0% (48/100)
Viral	26.0% (26/100)
Hepatitis B	10.0% (10/100)
Hepatitis C	16.0% (16/100)
NASH/NAFLD	22.0% (22/100)
Alcoholic	12.0% (12/100)
Other	4.0% (4/100)
Metabolic	3.0% (3/100)
[1] Subjects may have more than one pre-existing liver disease.	

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 100 treated patients available for the 1-25 months evaluation. The key safety outcomes for this study are presented below in Tables 3 to 6. Adverse effects are reported in Tables 3 to 5.

Adverse effects that occurred in the PMA clinical study:

As shown in Table 3 below, a total of 604 adverse events (AEs) were reported in 87 subjects out of 100 subjects as of the interim analysis, the majority of which (62.4%) were CTCAE grade 1. As of the interim analysis, 53 completed their 12-month follow-up visit. A total of 90 AEs were of moderate severity or higher (CTCAE grade 3 or higher), including 64 grade 3 AEs, 13 grade 4 AEs, and 13 unrelated grade 5 (death) AEs. There were 89 serious adverse events (SAEs), of which 13 SAEs had an outcome of death; none was considered device-or-procedure-related. The most common cause of death was respiratory failure (4 subjects), followed by HCC or disease progression (3 subjects). The cause of death was unknown for 4 subjects. Four SAEs were both serious and device- and/or procedure-related, including two instances of abdominal pain, one instance of ascites,* and one instance of nausea.

As shown in Table 4 and Table 5, 26.0% (26/100) of subjects had a total of 43 AEs classified as related to device and 23.0% (23/100) subjects had a total of 44 AEs classified as related to procedure.

Table 3. DOORwaY[90] All Adverse Events Occurring in ≥ 5% of Subjects by Frequency and Grade 3-4

Preferred Term (PT) by System Organ Class (SOC)	All Grades		Grades 3-4	
	% (n/N) of All AEs (N = 604)	% (n/N) of All Subjects (N = 100)	% (n/N) of All AEs (N = 604)	% (n/N) of All Subjects (N = 100)
Gastrointestinal disorders				
Abdominal pain	5.1% (31/604)	24.0% (24/100)	0.3% (2/604)	2.0% (2/100)
Nausea	3.8% (23/604)	17.0% (17/100)	0.2% (1/604)	1.0% (1/100)
Constipation	3.0% (18/604)	15.0% (15/100)	0.0% (0/604)	0.0% (0/100)
Vomiting	1.8% (11/604)	11.0% (11/100)	0.0% (0/604)	0.0% (0/100)
Ascites*	1.2% (7/604)	6.0% (6/100)	1.0% (6/604)	5.0% (5/100)
Abdominal distension	1.0% (6/604)	6.0% (6/100)	0.0% (0/604)	0.0% (0/100)
Diarrhea	1.0% (6/604)	6.0% (6/100)	0.0% (0/604)	0.0% (0/100)

General disorders and administration site conditions				
Fatigue	7.5% (45/604)	39.0% (39/100)	0.0% (0/604)	0.0% (0/100)
Oedema peripheral	1.7% (10/604)	8.0% (8/100)	0.2% (1/604)	1.0% (1/100)
Metabolism and nutrition disorders				
Decreased appetite	3.3% (20/604)	19.0% (19/100)	0.2% (1/604)	1.0% (1/100)
Nervous system disorders				
Dizziness	1.8% (11/604)	8.0% (8/100)	0.0% (0/604)	0.0% (0/100)
Hepatic encephalopathy	1.3% (8/604)	7.0% (7/100)	0.5% (3/604)	3.0% (3/100)
Respiratory, thoracic, and mediastinal disorders				
Cough	2.3% (14/604)	13.0% (13/100)	0.0% (0/604)	0.0% (0/100)
Dyspnea	1.8% (11/604)	11.0% (11/100)	0.0% (0/604)	0.0% (0/100)
Respiratory failure	1.2% (7/604)	6.0% (6/100)	0.3% (2/604)	2.0% (2/100)
Investigations				
Weight decreased	1.7% (10/604)	8.0% (8/100)	0.0% (0/604)	0.0% (0/100)
Infections and infestations				
Corona virus infection	1.2% (7/604)	7.0% (7/100)	0.2% (1/604)	1.0% (1/100)
Musculoskeletal and connective tissue disorders				
Back pain	1.7% (10/604)	10.0% (10/100)	0.2% (1/604)	1.0% (1/100)
Injury, poisoning, and procedural complications				
Contusion	1.2% (7/604)	6.0% (6/100)	0.0% (0/604)	0.0% (0/100)
Skin and subcutaneous tissue disorders				
Pruritus	1.3% (8/604)	7.0% (7/100)	0.0% (0/604)	0.0% (0/100)
Renal and urinary disorders				
Dysuria	0.8% (5/604)	5.0% (5/100)	0.0% (0/604)	0.0% (0/100)
Pollakiuria	0.8% (5/604)	5.0% (5/100)	0.0% (0/604)	0.0% (0/100)
Psychiatric disorders				
Insomnia	1.7% (10/604)	10.0% (10/100)	0.0% (0/604)	0.0% (0/100)
Blood and lymphatic system disorders				
Anaemia	1.2% (7/604)	6.0% (6/100)	0.0% (0/604)	0.0% (0/100)

*The one serious, device related event of ascites was reassessed as REILD by the site investigator. The outcome of the event was "resolved."

Table 4. DOORwaY^{90} All Device Related Adverse Events by PT Frequency Occurring in ≥ 5% of Subjects

Preferred Term (PT)	% (n/N) of All Device Related AEs (N = 43)	% (n/N) of All Subjects (N = 100)
Abdominal pain	18.6% (8/43)	8.0% (8/100)
Vomiting	14.0% (6/43)	6.0% (6/100)
Nausea	11.6% (5/43)	5.0% (5/100)
Fatigue	25.6% (11/43)	11.0% (11/100)

Table 5. DOORwaY^{90} All Implant Procedure Related AEs by PT Frequency Occurring in ≥ 5% of Subjects

Preferred Term (PT)	% (n/N) of All Procedure Related (N = 44)	% (n/N) of All Subjects (N = 100)
Abdominal pain	20.5% (9/44)	7.0% (7/100)
Vomiting	13.6% (6/44)	6.0% (6/100)
Nausea	11.4% (5/44)	5.0% (5/100)
Fatigue	18.2% (8/44)	8.0% (8/100)

Liver Findings in DOORwaY^{90}

A liver toxicity analysis was performed by comparing baseline biomarker laboratory results with post procedure biomarkers at 1, 2, 4, 6, 9, and 12 month follow-up visits. At each follow-up visit, over 95% of subjects showed stable liver function post SIR-Spheres treatment with biomarkers (AST, ALT, Bilirubin, Albumin) within normal range.

Twenty-four (24) subjects experienced a grade 3 or higher event within 6 months per CTCAE v5.0 criteria. One (1) subject underwent liver resection, and 15 subjects received a liver transplant during study follow-up to date. A summary can be found below in Table 6.

Table 6. Liver Toxicity Analysis

Characteristic	% (n/N) of Subjects (N = 100)
Grade ≥ 3 toxicity (CTCAE v5.0)	
At 2 months	9.0% (9/100)
At 6 months	24.0% (24/100)

Characteristic	% (n/N) of Subjects (N = 100)
Incidence of liver resection	1.0% (1/100)
Time from procedure to liver resection	3.38 months
Incidence of liver transplant	15.0% (15/100)
Time to liver transplant or resection (months)	
N	15
Mean +/- SD	10.3 +/- 4.8
Median (Range)	10.3 (1.3-20.8)

Based on the DOORwaY^{90} study, the safety profile was consistent and in line with what is observed based on previous clinical trials and longstanding marketed use of SIR-Spheres® Y-90 resin microspheres. Most AEs reported in the DOORwaY^{90} study were not severe or serious in nature, required no invasive intervention and were resolved.

Intra-hepatic Technetium MAA Radiation Absorbed Doses

A total of 5 subjects were enrolled at a single site. The mean subject age was 62.2 ± 14.0 years (range 40.0 - 74.0 years) and 60% were male and 40% were female. The mean ^{99m}Tc-MAA activity administered was 150.0 ± 14.3 MBq. There were no procedure-related complications and no adverse events. Mean absorbed dose (mGy/GBq) to liver and non-critical organs were obtained. The largest mean dose was 127.6 ± 80.6 mGy/GBq to the liver within the treatment zone followed by 31.7 ± 31.4 mGy/GBq to the gallbladder. The whole-body effective dose was small (0.6 ± 0.6 mGy).

2. Effectiveness Results

The analysis of effectiveness was based on the 65 evaluable patients. Key effectiveness outcomes are presented in Table 7.

In DOORwaY^{90}, 98.5% (64/65) of subjects in the effectiveness cohort demonstrated response by localized mRECIST as adjudicated by the independent imaging core laboratory. The only subject who failed to show a response was due to unevaluable imaging, meaning that all subjects with evaluable imaging demonstrated response for a 100% rate of local tumor control. Among subjects demonstrating tumor response, 76.6% (49/64) showed DoR of at least 6 months as adjudicated by the independent imaging core laboratory, exceeding the 60% threshold for this co-primary endpoint. The DOORwaY^{90} study therefore met both of its co-primary endpoints, demonstrating significant clinical benefit in the studied population. Effectiveness results for ORR and DoR are summarized in Table 7. Confirmed response is defined as response observed in subsequent imaging at least 4 weeks after initial response. Since alpha allocated for the interim analysis was calculated as 0.007, the confidence intervals cited below are two-sided 99.3% confidence intervals.

Table 7. Effectiveness Results

Characteristics	Response (N = 65)	Confirmed Response (N = 65)
Overall response rate (ORR) through 9 months	98.5% (64/65) [88.6%, 100.0%]	90.8% (59/65) [77.0%, 97.7%]
Complete response (CR)	92.2% (59/64)	91.5% (54/59)
Partial response (PR)	7.8% (5/64)	8.5% (5/59)
Duration of response (DoR)		
N	64	59
Mean ± SD (days)	238.7 ± 106.9	258.9 ± 84.2
Median (range, days)	300.5 (0.0-375.0)	303.0 (51.0-375.0)
Percent with duration ≥ 6 months	76.6% (49/64)	83.1% (49/59)

3. Subgroup Analyses
   Analyses of the primary endpoints of ORR and DoR were performed for the following subgroups: age, sex, race, ethnicity, BCLC, Child-Pugh, pre-existing liver disease, sum of maximum tumor diameter, administration method, lesion count (single vs multiple), protocol deviations, and additional Y-90 treatment. No statistically significant differences in response were found for either endpoint between subgroups.

   The study was not specifically powered for all above subgroups.

4. Pediatric Extrapolation
   In this PMA Supplement, existing clinical data was 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. The pivotal clinical study included 28 clinical investigators of which 0 were full-time or part-time employees of the sponsor and 8 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 3
- Significant payment of other sorts: 6
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

FDA determined the information provided did raise questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Outside-the-US (OUS) clinical data

SIR-Spheres® Y-90 resin microspheres have been on the global market for over 20 years with a well understood and established safety profile. SIR-Spheres® Y-90 resin microspheres is used in more than 40 countries where regulatory approval has been obtained. In the EU, SIR-Spheres® Y-90 resin microspheres are approved for mCRC and HCC, and in the rest of world the device is approved for advanced non-operable liver cancer.

XIII. 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.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In DOORwaY^{90}, 98.5% (64/65) of subjects in the effectiveness cohort demonstrated response by localized mRECIST as adjudicated by the independent imaging core laboratory. The lone failure of this endpoint was due to unevaluable imaging, meaning that all subjects with evaluable imaging demonstrated response for a 100% rate of local tumor control. Among subjects demonstrating tumor response, 76.6% (49/64) showed DoR of at least 6 months as adjudicated by the independent imaging core laboratory, exceeding the 60% threshold for this co-primary endpoint. The DOORwaY^{90} study therefore met both of its co-primary endpoints, demonstrating significant clinical benefit in the studied population.

B. Safety Conclusions

The risks of the device are based on data collected in DOORwaY^{90} study conducted to support PMA Supplement approval as described above. The safety profile of SIR-Spheres treatment in DOORwaY^{90} was acceptable, with only four (4) device- or procedure-related SAEs observed among three (3) subjects in the safety cohort of 100 enrolled and treated subjects. The DOORwaY^{90} interim analysis collected and reported all AEs throughout study follow-up regardless of seriousness or relatedness; during the reporting period, 604 AEs were reported in 87 out of 100 patients. Within these, 90 AEs of CTCAE grade 3 or higher occurred in 36 subjects and 89 SAEs occurred in 39 subjects. None (0) of the 13 deaths reported in the study were related to the device or procedure. There were no (0) unanticipated adverse device effects (UADEs). Additionally, at each follow-up visit, over 95% of subjects showed stable liver function post SIR-Spheres treatment with biomarkers

(AST, ALT, Bilirubin, Albumin) within normal range. Based on the DOORwaY^{90} study, the safety profile is acceptable and is in line with what is expected based on the longstanding commercial history of the product.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the DOORwaY^{90} clinical study conducted to support PMA approval as described above. The probable benefits of the device are based on an interim analysis of data collected in the DOORwaY^{90} clinical study conducted to support PMA approval as described above. The benefits of SIRT with SIR-Spheres for the target HCC patient population are successfully demonstrated through the study's effectiveness data. Specifically, 98.5% of subjects in DOORwaY^{90} showed objective response based on localized mRECIST criteria, and among the subjects with a response, 76.6% of the subjects in DOORwaY^{90} had a DoR of equal to or over 6 months. Benefit was also demonstrated using confirmed response, as 90.8% of subjects showed objective response, and among the subjects with a response, 83.1% of subjects had a DoR of equal to or over 6 months. These effectiveness results successfully achieved the statistical success criteria, a lower limit of 99.3% CI for best ORR by localized mRECIST >40%, and DoR by localized mRECIST >6 months for ≥60% of responders. Additionally, subjects that presented with multifocal HCC showed 100.0% (14/14) objective response and 71.4% (10/14) had DoR of equal to or over 6 months, supporting the benefit of SIR-Spheres in this treatment cohort. Further, all imaging which was evaluable by the independent core laboratory showed positive response, either complete or partial; there were no observations of disease progression by localized mRECIST in the treated hepatic lesions in any subject at any point during follow-up, as confirmed by the independent core laboratory. That is DOORwaY^{90} reported a best response of 100% local tumor control as adjudicated.

The probable risks of the device are based on data collected in the DOORwaY^{90} study to support PMA Supplement approval. The risks of SIRT with SIR-Spheres are well established for the target HCC patient population. SIR-Spheres has commercial use of over 20 years in >100,000 patient doses. The formal analysis of the DOORwaY^{90} study data available as of the interim analysis corroborates an acceptable safety profile. Inclusion of HCC to the indications for SIR-Spheres was not found to introduce any new patient-safety risks or impact existing device-related risks based on the totality of evidence presented.

At the time of review, 53 patients had not completed the two-year follow up as per the DOORwaY^{90} protocol. However, given the data met the pre-specified endpoints, and the safety profile was similar to the known safety profile of SIR-Spheres, the data allowed for a determination of a reasonable assurance of safety and effectiveness. In conclusion, given the available information above, the data support that for the indication for use of the device 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. Based on the information presented in this assessment, the totality of evidence supports the use of SIR-Spheres® Y-90 resin microspheres for the local tumor control of unresectable HCC in patients with no macrovascular invasion, Child Pugh-A cirrhosis, well-compensated liver function, and good performance status. The benefits associated with the use of the SIR-Spheres® Y-90 resin microspheres device outweigh the risks for the treatment of HCC in the intended patient population.

XV. CDRH DECISION

CDRH issued an approval order on 07/01/2025.

The final clinical conditions of approval cited in the approval order are described below.

Continued Follow up of the IDE Study (DOORwaY^{90}) Subjects: This study is a single arm, multicenter, prospective study that consists of continued follow-up of all available subjects from the IDE Pivotal Study (STX2001, revision F). The study evaluates the safety and effectiveness of selective internal radiation therapy (SIRT) using SIR-Spheres® Y-90 resin microspheres in hepatocellular carcinoma (HCC) patients. A total of 100 subjects were enrolled. Thirty (30) subjects exited the study early. Of the 70 remaining subjects, 17 subjects have completed the full 2 years of follow-up. The remaining subjects will complete the full 2-year follow up plan set up in the IDE study protocol. Clinical outcomes include objective response rate (ORR) and duration of response (DoR). The endpoints will be analyzed against preset success criteria including 1) Lower limit of 95% confidence interval (CI) for ORR by localized mRECIST >40% and 2) DoR ≥6 months for ≥60% of responders. 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 interim report.

XVI. 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.

XVII. REFERENCES

None