

# THERASPHERE™ Y-90 Glass Microspheres

## DOSISPHERE-01 Trial Summary

Level 1 evidence of 26.7 month overall survival for HCC patients treated with TheraSphere using personalized dosimetry compared to 10.7 months with standard single compartment dosimetry.

### STUDY OBJECTIVE:

Multi-center, prospective, randomized, investigator-sponsored phase II trial designed to compare the clinical outcomes of SIRT with TheraSphere in patients with advanced HCC using two pre-treatment dosimetry determination methods: (1) Standard, single-compartment dosimetry (SDA); defined as a uniform distribution of absorbed dose within the perfused volume – both tumor and normal liver or (2) Personalized dosimetry (PDA); defined as multi-compartment Y-90 distribution of absorbed dose within the perfused volume that accounts for preferential blood flow into the tumor compared with normal parenchyma.

### PRIMARY ENDPOINT:

Response rate of the index lesion at Month 3 according to EASL criteria using a mITT population\* by investigator assessment.

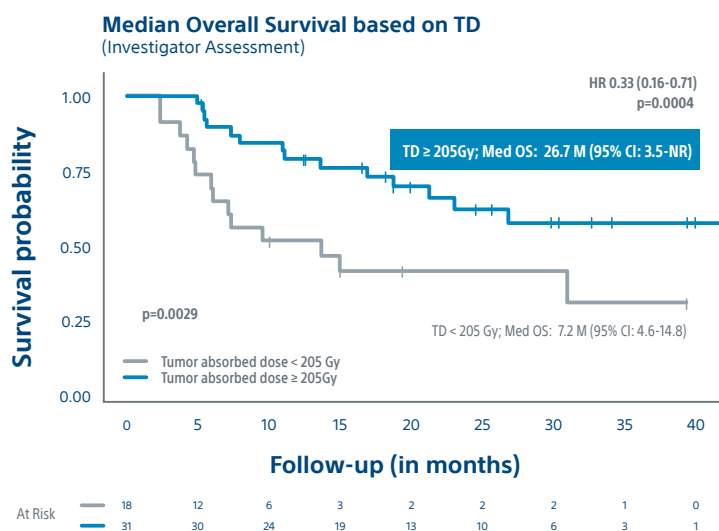
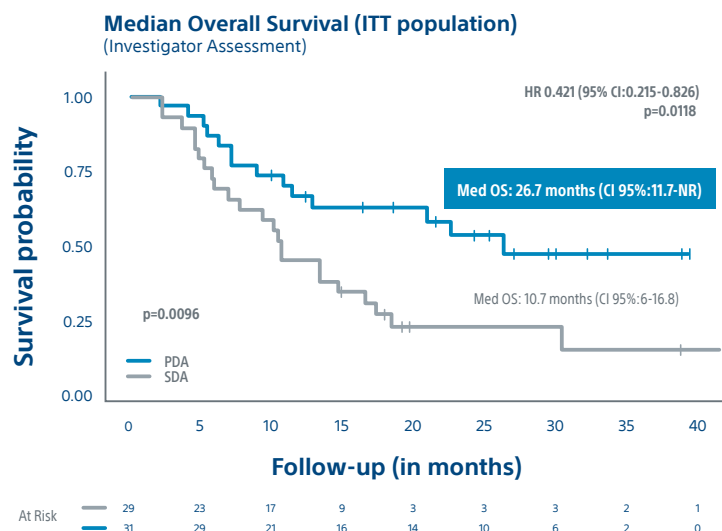
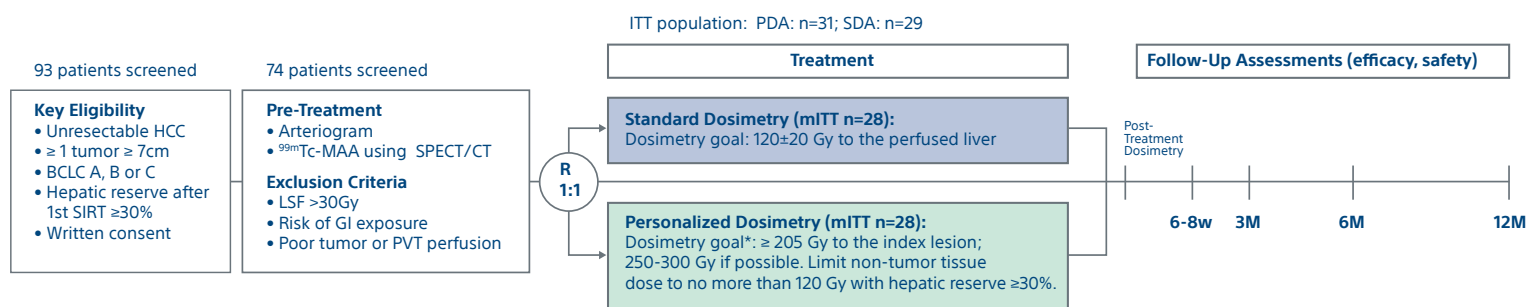
\*mITT: randomized and treated patients

### MAIN SECONDARY ENDPOINTS:

Overall Survival | PFS | Dose-response relationship | Safety

### STUDY DESIGN:

Multi-centre, randomized (1:1), prospective, phase II study



# DOSISPHERE-01 Trial Summary | 12 month results

## PATIENT DEMOGRAPHICS (mITT population)

Parameter	PDA (n=28)	SDA (n=28)
Age (median±SD)	64.8±10.1	62.5±13.1
Male (%)	92.9	92.9
Underlying cirrhosis (%)	85.7	85.7
Child-Pugh Status (%)	CP A5: 78.6 CP A6: 21.4 CP B7: 0	CP A5: 78.6 CP A6: 21.4 CP B7: 0
Mean Total Bilirubin (µM/L±SD)	14.63±6.43	13.63±5.78
ECOG (%)	0: 57.1 1: 42.9	0: 46.4 1: 53.6
PVT present (%)	67.9	75.0
Index lesion (mean, cm)	10.36±2.44	10.67±2.79
Tumoral involvement (mean±SD)	23.01±13.95	23.97±14.2

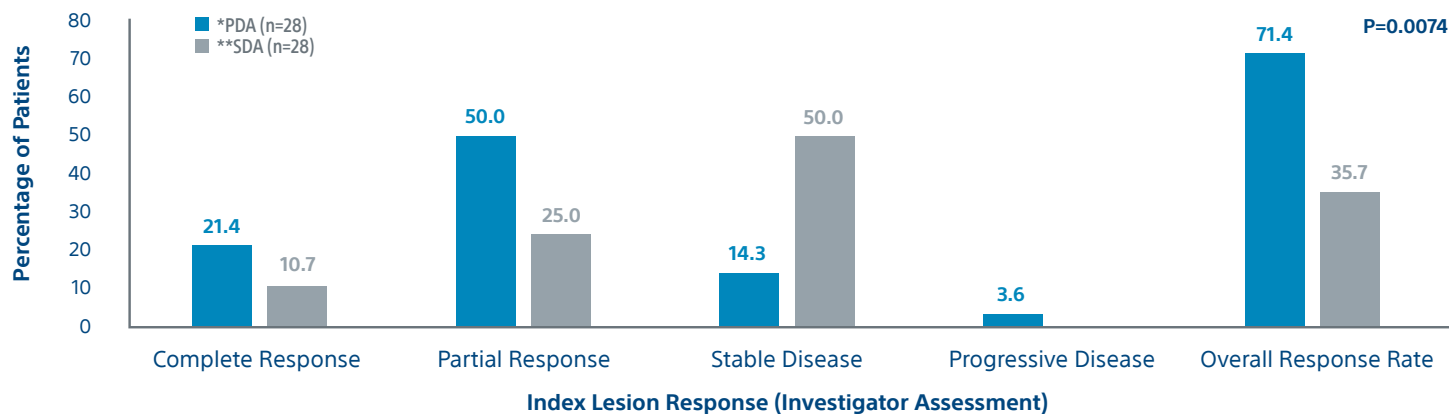
\*No significant difference in baseline characteristics between groups

## TREATMENT CHARACTERISTICS AND DOSIMETRY (mITT population)

Investigator Assessments	PDA arm (n=28)	SDA arm (n=28)	P value
Number of Y-90 glass microspheres treatment	One treatment, n=26 Two treatments, n=2	One treatment, n=24 Two treatments, n=4	ns
Activity administered GBq (mean, min-max)	3.98 (1.3-9.6)	2.72 (1.0-5.1)	ns
AD to perfused liver (Gy) Mean (±SD)	178.4±59.9	124.5±27.3	0.0001
% of patients with AD to perfused liver > 150 Gy	67.9	7.1	<0.0001
AD to index lesion (Gy) Mean (±SD)	342.6±131.5	221.3±139.4	0.0033
% of patients with AD to index lesion > 205 Gy	92.8	32.1	0.0008
AD to perfused normal tissue (Gy) Mean (±SD)	94.7±30.3	64.5±36.6	0.0038

\*AD=absorbed dose

## PRIMARY END POINT: INDEX LESION RESPONSE RATE AT 3 MONTHS USING EASL IN THE mITT POPULATION



\*reasons for censoring: received another anti-cancer treatment before M3 evaluation (n=2), no evaluation at M3 evaluation (n=1) (10.7%)

\*\*reasons for censoring: Early deaths (before M3) (n=2), no evaluation at M3 (n=1), start another anti-cancer treatment before M3 evaluation (n=1) (14.3%)

## LIVER ADVERSE EVENTS (Grade ≥3) Related to Y90\*

	PDA (n=35)	SDA (N=21)
Patients with ≥ 1 AE	3 (8.6%)	3 (14.3%)
Death	1 (2.9%)	1 (4.8%)
Liver AEs	4 (11.4%)	5 (23.8%)
Ascites	1 (2.9%)	1 (4.8%)
Encephalopathy	0	0
GI hemorrhage	0	2 (4.8%)
Bilirubin increase/jaundice	1 (2.9%)	2 (9.5%)
Hepatic failure	2 (5.7%)	0

\*patients allocated to either PDA or SDA based on treatment received (dose received) versus allocation by randomization

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### TheaSphere Y-90 Microspheres

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions. INTENDED USE/INDICATIONS FOR USE: TheaSphere is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis, occlusion when clinical evaluation warrants the treatment. **Humanitarian Device**: Authorized by Federal Law for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion when clinical evaluation warrants the treatment. The effectiveness of this device for this use has not been demonstrated. **CONTRAINDICATIONS**: The use of TheaSphere is contraindicated in patients whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques (see Item 1 under INDIVIDUALIZATION OF TREATMENT)† who show shunting of blood to the lungs that could result in delivery of greater than 15.5 mCi of yttrium-90 to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment (see Item 2 under INDIVIDUALIZATION OF TREATMENT)‡ in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities or bleeding diathesis • who have severe liver dysfunction or pulmonary insufficiency, and • who present with complete occlusion of the main portal vein (see Item 3 under INDIVIDUALIZATION OF TREATMENT)§ INDIVIDUALIZATION OF TREATMENT: 1. Gastrointestinal ulceration is a potential complication of misplaced deposition of radioactive microspheres. It is likely that inadvertent deposition of yttrium-90 microspheres in the terminal gastric vascular bed reflects the backflow of microspheres during administration or shunting through aberrant small vessels within the cirrhotic liver or tumor. Although angiographic occlusion techniques and the use of vasoactive drugs may reduce gastrointestinal shunting, their effectiveness is uncertain. If such flow is present and cannot be corrected using established angiographic techniques, the patient is disqualified from treatment. When the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment, TheaSphere may be administered. 2. In some patients, part of the hepatic arterial blood supply bypasses the capillary bed and flows directly to the venous system. This may be associated with pathological abnormalities of the liver. For such patients, a fraction of microspheres injected into the hepatic artery will not be embolized in the liver but will flow to the heart and subsequently be deposited into the lungs. As the product (a of the bypass fraction, F, and the injected activity, A, increases the potential for delivering a damaging dose of radiation to the lungs increases. Consequently, it is essential that F be measured before use of this product. This procedure is performed by injecting a tracer dose of Tc-99m MAA and observing with an Anger camera. The observed radiation from the lung field, divided by the total radiation observed by the camera is a measure of F. The product of F and A is then a measure of the activity that will be deposited into the lungs. ‡ Based on clinical study experience [15, 16] with radioactive microspheres and TheaSphere in HCC treatments, an upper limit of F of 0.10 (10%) is recommended. The estimated dose (D) to the lungs is equal to A(GBq) x F x 20, assuming the total mass of both lungs to be 1 kg [24]. An upper limit of dose to the lungs from a single TheaSphere treatment is 30 Gy. § Portal vein thrombosis (PVT) is observed in over 40% of HCC patients who are potential candidates for TheaSphere treatment [34]. For patients presenting with PVT, the clinician should weigh the risk versus benefit of yttrium-90 microsphere treatment. In a retrospective analysis of 25 patients presenting with branch or partial portal vein thrombosis, there was no increase in hepatic failure, hepatic encephalopathy, worsening of pre-existing portal hypertension, or extension of pre-existing portal vein occlusion following treatment with TheaSphere [35]. The most common adverse event observed after TheaSphere treatment in HCC patients presenting with PVT was elevated bilirubin. In all cases, elevated bilirubin was not treatment related but was attributed to progression of liver disease or cirrhosis [36]. Patients who present with PVT and symptoms of severe portal hypertension are at risk of liver decompensation and the risk versus benefit should be weighed accordingly. Patients presenting with complete occlusion of the main portal vein should not be considered for treatment due to the higher risk of liver failure, and potential complications (e.g. mesenteric infarct, necrosis, varical bleeding, ascites) associated with this condition. **PRECAUTIONS**: A retrospective study of 121 patients from 5 clinical trials has shown that the following 5 Pre-treatment High Risk Factors have been associated with at least 8% of all serious adverse events that were possibly related to use of the device and with 11 of the 12 deaths that were possibly related to use of the device: infiltrative tumor type • "Bull disease" (tumor volume > 70% of the target liver volume, or tumor nodules too numerous to count) • AST or ALT > 5 times ULN • bilirubin > 2 mg/dL • tumor volume > 50% combined with an albumin < 3 g/dL • The physician should always take the above-noted Pre-treatment High Risk Factors into consideration for each patient when making decisions regarding the use of TheaSphere for treatment. Radioactive products should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides. Adequate shielding and precautions for handling radioactive material must be maintained. As in the use of any radioactive material, care should be taken to ensure minimum radiation exposure to the patient, extraneous to the therapeutic objective, and to ensure minimum radiation exposure to workers and others in contact with the patient. Since adequate studies have not been performed in animals to determine whether this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards. Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses. Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately and the area monitored for contamination at the end of the procedure. The TheaSphere dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The TheaSphere dose vial should always be stored in a shielded location away from personnel. **ADVERSE REACTIONS**: Based on clinical and preclinical animal experience with TheaSphere and other yttrium-90 microspheres, certain adverse reactions have been identified [4-6, 15, 16, 17, 18]. Serious adverse events that occurred under clinical studies and that were defined following the onset of menses, are summarized in Table 1. Based on pooled data to 2004, in addition to these serious adverse events, symptoms like depression, which may be graded as moderate to severe but with no clinical sequelae, is expected to occur in some patients. The introduction of microspheres into the vasculature of the stomach, duodenum or other organs of the gastrointestinal tract may cause chronic pain, ulceration and bleeding. Microsphere shunting to the lungs may cause edema and fibrosis that may not be reversible. Extrahepatic shunting may be identified through the injection of Tc-99m MAA into the hepatic artery [19, 20]. Flow of radioactivity to the gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [21]. In addition, placement of the delivery catheter in the hepatic branch distal to collateral vessels provides a safety margin with respect to inadvertent deposition of microspheres. Some adverse events observed may be explained by the effect of attenuated radiation from the treated liver. Pleural effusion may be caused by attenuated radiation when the treated tumor is positioned proximal to the base of the lung. Similarly, treatment of tumors in the left lobe of the liver, in proximity to the gut, may explain some of the gastrointestinal events observed. Relative attenuated radiation effects to extrahepatic structures have generally been found to resolve over time. The use of this product leads to irradiation of both tumorous and normal liver tissue. As a result, patients with diseases that compromise the functioning of their normal liver have a higher incidence of liver-related serious adverse events in clinical trials. A retrospective study of 121 patients from 5 clinical trials has shown that the following 5 Pre-treatment High Risk Factors have been associated with at least 48% of all serious adverse events that were possibly related to use of the device and with 11 of the 12 deaths that were possibly related to use of the device: infiltrative tumor type • "Bull disease" (tumor volume > 70% of the target liver volume, or tumor nodules too numerous to count) • AST or ALT > 5 times ULN • bilirubin > 2 mg/dL • tumor volume > 50% combined with an albumin < 3 g/dL. Note: Dose to the liver did not exceed 150 Gy. The physician should always take the above-noted Pre-treatment High Risk Factors into consideration for each patient when making decisions regarding the use of TheaSphere for treatment. TheaSphere is a registered trademark of Theragnostics Corporation used under license by Biocompatibles UK Ltd.



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