SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Trade Name:	OncoSil™
Device Procode:	SIY
Applicant's Name and Address:	OncoSil Medical Limited Level 5, 7 Eden Park Drive Macquarie Park NSW 2113 Australia
Date(s) of Panel Recommendation:	None
Humanitarian Device Exemption (HDE) Number:	H200002
Humanitarian Use Device (HUD) Designation Number:	HUD # 18-0415
Date of HUD Designation:	November 19, 2018
Date of Notice of Approval to Applicant:	August 14, 2026

II. INDICATIONS FOR USE

OncoSil™ is intended for intratumoral implantation into a solid tumor via injection under endoscopic ultrasound guidance.

OncoSil™ is indicated for the treatment of patients with distal cholangiocarcinoma (dCCA) that is both unresectable* and non-metastatic, as an adjunct to systemic therapy.

OncoSil™ is indicated for the treatment of patients over 21 years of age.

Implantable components of OncoSil™ are supplied sterile and are intended for single-patient, single-use.

* locally advanced and/or unfit for surgery

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for the treatment of intrahepatic cholangiocarcinoma (ICC) and distal cholangiocarcinoma (dCCA). It was modified for the HDE approval because the revised indications for use (IFU) statement more clearly identifies the patient population in which the safety and probable benefit of the device is supported by the available clinical data. The patient population in the modified IFU falls within the patient

population granted by the HUD designation.

III. CONTRAINDICATIONS

- OncoSil™ is contraindicated in patients whose tumor is considered resectable, except for patients considered unfit for surgical resection.
- OncoSil™ is contraindicated in patients who have a known history of hypersensitivity to silicon or phosphorous.
- OncoSil™ is contraindicated where endoscopic ultrasound (EUS) directed implantation is considered hazardous (refer to *PRECAUTIONS*).
- Implantation of OncoSil™ should not occur in the following special situations:
    - Presence of multiple collateral vessels surrounding or adjacent to the target tumor.
    - Presence (or significant risk) of varices near the target tumor.
- Chemotherapy administration is contraindicated within 48 hours before or after OncoSil™ administration.
- OncoSil™ is contraindicated in patients with abnormal liver function tests.
- Retreatment with OncoSil™ is contraindicated.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the OncoSil™ labeling.

V. DEVICE DESCRIPTION

The OncoSil™ System consists of:

- A sterile, single-use vial of OncoSil™ Phosphorous-32 Microparticles;
- 2 sterile vials of OncoSil™ Diluent;
- 1 empty sterilized P6 vial for dilution of suspension of OncoSil™; and
- 1 empty lead pot for dilution of suspension of OncoSil™.

The OncoSil™ Phosphorous-32 Microparticles (hereafter Microparticles) and OncoSil™ Diluent (hereafter Diluent) are mixed per the Instructions for Use to produce the OncoSil™ Device (hereafter OncoSil™).

OncoSil™ is a brachytherapy device used to deliver a planned dose of 100 Gy directly into a tumor via direct injection (intratumoral implantation) under ultrasound-guided endoscopy using a biopsy needle that has been advanced within the echoendoscope. Once implanted in the target tumor, placement of the device can be assessed via Single-Photon Emission Computed Tomography (SPECT-CT) Bremsstrahlung imaging. The SPECT imaging assessment for P-32 activity localization is performed qualitatively only.

The Microparticles contain Phosphorous-32, a pure beta-emitter radioisotope with a physical half-life of 14.27 days. The maximum energy of the emitted beta particles is 1.711 MeV. The average energy of the emitted beta particles is 0.6950 MeV. The

maximum range of emissions in tissue is 8.2 mm. The average range of emissions in tissue is 2.76 mm. In therapeutic use, 98% of the radiation is delivered within 81 days. The Microparticles are a permanent implant. The Microparticles are manufactured for clinical use by combining highly pure silicon with phosphorous, to produce grey-black Microparticles with a diameter range of 28 to 32 microns, which are then irradiated to convert P-31 (a stable isotope of phosphorous) into P-32 (a radioactive β-emitting isotope of phosphorus).

The Microparticles are provided in individually crimp-sealed vials, containing 250 ± 10% MBq at 11:00 AM Greenwich Mean Time or 6:00 AM Eastern Standard Time. Each individual vial of Microparticles is placed inside an acrylic-lined lead pot to shield personnel from radiation during shipping and handling.

The Diluent performs as a carrier to facilitate implantation of the Microparticles into the target treatment tumor. The Diluent is provided in individually crimp-sealed vials each containing approximately 9 mL of Diluent.

The implantable components of OncoSil™ are supplied sterile and are intended for single-patient, single-use.

OncoSil™ does not incorporate any metallic components or material or ingredient derived from medicinal, human, animal or recombinant origin.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Due to the rarity of distal cholangiocarcinoma (dCCA) it is subsumed under the broader category of biliary tract cancer (BTC) or extrahepatic cholangiocarcinoma (eCCA); the clinical literature and practice guidelines are not specific to dCCA. Treatments for dCCA follow the guidelines for BTC/eCCA and are based on the individual patient presentation.

Endoscopic retrograde cholangiopancreatography with transpapillary stenting remains the standard first-line approach for biliary drainage in distal cholangiocarcinoma, but EUS-guided choledochoduodenostomy (EUS-CDS) is emerging as a viable primary alternative with specific technical advantages.

Treatments are determined by whether the primary tumor is resectable or unresectable and whether metastatic disease is present. For tumors which have not spread and can be completely removed, surgery is a potentially curative option. Treatments for unresectable disease may include systemic chemoimmunotherapy, chemotherapy, chemoradiation, a combination of chemotherapy and chemoradiation, photodynamic therapy with stenting, radiofrequency ablation and intraluminal brachytherapy, or palliative radiation therapy. Bile duct occlusion is a common symptom during the dCCA disease course, resulting in jaundice and significant pain. Palliative procedures for relief of symptoms include biliary drainage and stent placement, biliary bypass surgery, external radiation therapy or radiofrequency ablation and photodynamic therapy.

VII. MARKETING HISTORY

OncoSil™ has been CE marked since March 2020 and under MDR Certification since January 2024.

Currently, the list of countries where OncoSil™ is approved includes: Australia, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia (Czech Republic), Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Poland, Portugal, Romania, Saudi Arabia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Türkiye, and United Kingdom.

OncoSil™ has not been withdrawn from marketing for any reason relating to the safety and probable benefit of the device.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (AEs) (i.e., complications) considered to have a possible, probable, or definite causal relationship with the use of the device (OncoSil™ and/or the implantation procedure).

- Procedure-related pain and/or discomfort, e.g., oropharyngeal pain, dyspepsia
- Abdominal pain and/or discomfort
- Nausea
- Vomiting
- Lethargy/fatigue
- Fever
- Abnormal liver function test
- Diarrhea
- Neutropenia
- Hypokalemia
- Pulmonary embolism
- Lymphopenia

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

IX. SUMMARY OF NON-CLINICAL STUDIES

The objectives of the non-clinical studies were to (a) ensure the device is biocompatible based on the nature/duration of device contact, (b) conduct non-clinical testing to characterize and evaluate the performance and functionality of the device, (c) to validate the sterilization of the device, and (d) to demonstrate that the device has continued performance to support a shelf-life of two (2) years, with its current packaging.

A. Biocompatibility and Non-Clinical Studies

Testing described in this section was conducted on BioSilicon or Biosilicon High P (size specified as either 20 or 30 micron), with iterations of the device also referred to as ^{32}P BioSilicon™. The device was subsequently renamed to OncoSil™. BioSilicon 20 micron has the same chemical composition and structure as OncoSil Microparticles but the particle size distribution has a mean of 20 microns, and not 30 microns as intended for clinical use. Testing was conducted with the non-radioactive form (unless otherwise specified).

Non-clinical testing included performance testing in pancreas and liver models, with the latter being used for early device design. Additionally, since the animal studies were conducted for a liver indication during the early development of OncoSil™, Microparticles were implanted through coaxial introducer/implantation needles using a percutaneous approach. Given anatomic complexities of the pig anatomy, variations in operative positioning, and the injection of ^{32}P BioSilicon™ into normal hepatic parenchyma, there were occurrence of needle misplacement which were found to result in non-target deposition of ^{32}P BioSilicon™ outside the target liver anatomy. The current implantation technique, which uses ultrasound-guided endoscopy through a biopsy needle to deliver Microparticles intratumorally, was incorporated as a mitigation for inadvertent deposition of OncoSil™ outside the target.

Biocompatibility testing for materials used to manufacture OncoSil™ were performed in accordance with ISO 10993-1, *"Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process."* Table 1 outlines testing leveraged to specifically address biocompatibility endpoints. Additional testing from the other non-clinical studies (detailed further below) were also leveraged in support of biocompatibility assessments. In addition to the testing outlined below, supplemental biological risk assessment was leveraged. This assessment reviewed available data on the materials of construction and the manufacturing process for the device. This biological risk assessment was informed by information gathered from published literature on the raw materials of construction of the device, manufacturing process data, and on existing preclinical studies and clinical data on the device.

Table 1. Biocompatibility Evaluation

Test	Method/Report	Purpose	Results/Conclusion
Cytotoxicity	Elution Method (MRC-5 Cells)	To determine potential cytotoxicity when Medical Research Council cell strain 5 (MRC-5) cells (human embryonic lung diploid fibroblasts) are exposed to implant extracts.	Non-Cytotoxic
	ISO MTS cytotoxicity test	To determine potential cytotoxicity when L-929 mouse fibroblast cells are exposed to implant extracts.	Non-Cytotoxic
Sensitization	Local lymph node assay	To assess the skin sensitization potential using the murine local lymph node assay.	Non-sensitizer
Pyrogenicity	Rabbit Pyrogen Test	To evaluate implant extracts for the potential of inducing a pyrogenic response in rabbits.	Non-Pyrogenic
Systemic Toxicity	14 Day Pilot Toxicity Study in the Rat	To evaluate the toxicity and Maximum Tolerated Dose (MTD) of Porous Silicon and to provide information to aid the selection of dose levels in subsequent dose toxicity studies.	The maximum suggested dose level of porous silicon when administered by the subcutaneous or intraperitoneal route was evaluated.
	Single intraperitoneal dose toxicity study in the rat followed by 14-day observation	To assess toxicity of different BioSilicon dose levels following a single dose via the intraperitoneal route.	No systemic toxicity noted at the varying dose levels. The No Adverse Effect Level (NOAEL) was determined to be 50 mg/kg/day.
Genotoxicity	Bacterial Reverse Mutation Test	To assess potential for test article extract to induce a genotoxic response.	No evidence of mutagenic activity observed.
	In vitro mammalian chromosome aberration test in CHL (Chinese Hamster Lung) cells	To assess potential for test article extract to induce a genotoxic response.	No evidence of clastogenic activity observed.
Hemocompatibility	Hemolysis Test	To assess device interaction with blood.	Non-hemolytic
	Blood coagulation compatibility test		No effect on the activation of blood coagulation systems as determined by the prothrombin time, activated partial thromboplastin time and fibrinogen levels.

Table 2 provides an overview of additional non-clinical studies leveraged to inform and/or supplement the above biocompatibility testing (e.g., implantation), inform device modifications, and assess performance. While these generally represent earlier

iterations of the device as described above, the studies helped provide relevant information, such as the importance of proper injection for device localization.

Table 2. Additional In Vitro and In Vivo Non-Clinical Testing

Method/Report	Purpose/Results
^{32}P BioSilicon™ 20 Micron High P: Disposition Studies in the Rat After Single Intravenous and Subcutaneous Administration (PSP002, wherein PSP refers to testing of ^{32}P BioSilicon High P samples)	The purpose of this study was to investigate pharmacokinetics, absorption, distribution, and excretion of the 20 micron BioSilicon (radioactive). Following intravenous injection, no adverse clinical signs were observed over a 24 hr period. The particles remain in the lungs, showing little sign of being solubilized, redistributed or excreted over a period of 168 hours. Following subcutaneous administration, the material remained localized until approximately 48 hr, after which solubilization was observed. Radioactivity appeared in the blood from 72 h, and increased in concentration until about 336 h. <1% was found in tissues at 336 h. The pathway of elimination was postulated to be via the lymph and blood vessels to the kidney as ^{32}Phosphorus or ^{32}Phosphate.
^{32}P BioSilicon™ 30 Micron High P: Disposition Studies in the Rat After Single Intravenous and Subcutaneous Administration (PSP014)	The purpose of this study was to obtain information on the rate and extent of urinary excretion of radioactivity from the 30 micron BioSilicon (radioactive) and the distribution of radioactivity in selected body tissues. The study added to information gained in PSP002: The steady excretion of radioactivity in urine up to 168 hours post-dose in the PSP002 study was repeated and extended in PSP014. The rate of elimination of test material from the dose site and quantity appearing in urine was greater for the smaller 20 micron particles than the 30 micron particles. However, ^{32}P representing between 0.5% and 1% of injected activity was excreted daily until the last collection time of 672 hours post administration, when a total of about 17% of the total administered activity had been excreted via the urine. There was a low level of uptake in tissues generally – up to 4.62% in the skeleton was estimated but less than 0.3% of injected radioactivity in either the kidney, liver or spleen, the only other tissues analyzed. Concentrations of ^{32}P in bone increased until 672 hours post-dose, decreasing thereafter, showing that solubilization of the test material and release of ^{32}P as inorganic phosphate salt from bone after this time was a likely mechanism of distribution and excretion of this isotope from bone.
In Vitro Investigation of Release Kinetics of ^{32}P-BioSilicon in Four Matrices (PSP003)	The purpose of this study was to investigate the release kinetics of radioactive BioSilicon in various matrices (release kinetics). Observed solubilization varied depending on the tested media (ultrapure water, isotonic saline, or human plasma). Minimal solubilization of the test material occurred in ultrapure water or formulant (<0.5%) under all conditions time tested. Isotonic saline (pH 7.4) exhibited greater amounts of solubilization of radioactivity between 504 and 672 hours of incubation at 370°C when 1.3% was found in the supernatant. Human plasma contained relatively constant levels of radioactivity in the supernatant until 336 hours, when significant amounts of radioactivity were found. Levels rose from 19.32 ± 29.06% at 336 hours to 96.25 ± 24.20% at 672 hours.
Study of BioSilicon as Intratumoral Unsealed Radioactive Source Therapy (^{32}P SGH (Singapore General Hospital) Study I (Mouse))	The aims of the study were to implant BioSilicon in transplanted tumors using mouse models and to study the effects of local treatment using BioSilicon implants on growth of transplanted tumors in mice by time-dependent observation of tumor response compared to a control. The presence of radioactivity was noted to suppress the growth of tumor cells.

Effect of ^{32}P BioSilicon™ on the Growth of Transplanted Hep G2 Cells and 2119 Tumor Cells in Nude Mice (^{32}P SGH Study II (Mouse))	The purpose of this study was to investigate the effects of local treatment of 20 micron BioSilicon (radioactive) on human liver cells (Hep G2) and human pancreatic tumor cells (2119) implanted in mice. The presence of radioactivity was noted to suppress the growth of tumor cells.
A Performance Administration Study for Intrahepatic Implantation of ^{32}P BioSilicon™ in the Pig (^{32}P SGH Study III (Pig))	The purpose of this study was to optimize the intrahepatic implantation procedure for administration of the 20 micron BioSilicon (radioactive). Measurement of circulating 32-Phosphorus radioactivity within the first 30 days for the four pigs indicated some leakage (ranging from 3.5 to 15.6%).
A Performance Administration Study using a Multi-Implanter for Intrahepatic Implantation of ^{32}P BioSilicon™ in the Pig (^{32}P SGH Study IV (Pig))	The primary aim of the study was to assess the performance of prototype needle placement in implantation of 30 micron BioSilicon (radioactive) within health pig liver. BioSilicon was delivered at three dose levels to three groups of animals respectively. Misplacement of the needle may lead to delivery outside the target and into surrounding tissues. Information from this study was also leveraged in support of biocompatibility endpoints (implantation, chronic toxicity).
Analysis of Pig Blood and Urine Samples from ^{32}P SGH Study IV (PSP015)	The purpose of this study was to obtain information on the absorption of phosphorous-containing material from the device using blood and urine samples obtained from the ^{32}P SGH Study IV (Pig) study. Radioactivity was quantifiable in some blood samples from Pigs 1-2 and 4-6, reaching maximum concentrations at Day 39 and Day 21, respectively. Radioactivity was quantifiable in most of the urine samples supplied and, for each set of animals, fluctuated markedly throughout the collection period, such that the time when maximum concentrations occurred varied from 4–66 days post-dose. For all animals in the study, radioactivity was detectable in urine at or after 21 days post-dose. It was concluded that there is some release of radiolabelled phosphorus from the ^{32}P-BioSilicon™ 30 Micron High P administered during the performance administration study ^{32}P SGH Study IV, at least part of which is subject to urinary excretion.
Performance Assessment of an UltraSonic Gastrovideoscope for Brachytherapy Implantation of BioSilicon in Pig Pancreas (^{32}P SGH Study VII (Pig))	The study was conducted to determine the feasibility and practicality of an endoscopic ultrasound-guided (EUS) implantation of 30 micron BioSilicon in the normal pancreas of healthy pigs. No practical difficulties were observed during the implantation procedure.

Leakage Testing (ISO 9978)	The purpose of this test was to determine the release of ^{32}P activity from OncoSil™ phosphorus silicon alloy microparticles using the immersion method (hot liquid) from ISO 9978 "*Radiation protection — Sealed sources — Leakage test methods*". The test results indicated an average of 23.67 Bq which was less than the acceptance criterion of < 200 Bq ^{32}P.

B. Sterilization

The implantable components of OncoSil™ are supplied sterile and are intended for single-patient, single-use. Both the Microparticles and Diluent are sterilized using moist heat in accordance with ISO 17665-1, "*Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*". The Microparticles and Diluent have been validated to achieve sterility assurance level (SAL) 10^{-6}. Pyrogen, bioburden, and container closure integrity testing were conducted, and all sterilization criteria were met.

C. Shelf-Life and Packaging

Shelf-life studies were conducted to support the selected shelf life of the Diluent and supported a shelf life of 24 months when stored at 25°C.

Shelf-life for the OncoSil™ Microparticles is 7 days from reference date, based upon acceptable activity with P-32 half-life of 14.27 days.

The sterile barrier has been validated in accordance with ISO 11607-1:2019 "*Packaging for terminally sterilized medical devices* ***- Part 1:*** *Requirements for materials, sterile barrier systems and packaging systems"*.

The packaging was evaluated for compliance to storage and transportation requirements, and Type A general requirements of radiation shielding and all criteria were met.

X. SUMMARY OF CLINICAL INFORMATION

The safety and probable benefit of OncoSil™ was evaluated in four prospective, open label, single-arm studies (DB2-201, DB2-202, PanCO, and OncoPaC-1), as well as a retrospective real-world study (RAH/NZ) and a prospective real-world registry (OSPREY). The prospective studies were primarily leveraged to support the safety assessment, while the retrospective data were primarily leveraged to support the probable benefit assessment.

All available data on the safety and probable benefit of OncoSil™ for dCCA are based on studies of its use in patients with locally advanced pancreatic cancer (LAPC). Given the anatomic, physiological, and functional similarities of LAPC and dCCA, the data on LAPC are considered supportive of and clinically relevant to an assessment of safety and probable benefit of OncoSil™ for the dCCA population. Further, for studies of OncoSil™ in patients with LAPC, device use was combined with systemic therapy (FOLFIRINOX, gemcitabine + nab-paclitaxel, or gemcitabine).

A. Study Design

Tables 3 and 4 summarize the study design and inclusion/exclusion criteria for the four prospective studies and the two real world evidence (RWE) studies, respectively.

Table 3. Summary of Prospective Studies

Study Name	**DB2-201**	**DB2-202**	**PanCO**	**OncoPac-1**
Design	Single-arm prospective multi-center study	Single-arm prospective multi-center dose escalation study	Single-arm prospective multicenter study plus Meta-Analysis vs. chemo or CCRT	Single-arm prospective multi-center study
Primary Objective	To determine the safety of ^{32}P BioSilicon™ administered to patients with pancreatic cancer who are also receiving standard concomitant chemotherapy with gemcitabine at the current approved dose.	To determine the safety of ^{32}P BioSilicon administered at absorbed doses of 200 Gy and 400 Gy to patients with pancreatic cancer who are also receiving standard concomitant chemotherapy with gemcitabine at the current approved dose.	To further investigate the safety of the active implantable (radiological) medical device OncoSil™ when implanted intratumorally using Endoscopic Ultrasound Guidance in study participants with unresectable, locally advanced pancreatic cancer who are receiving either FOLFIRINOX or gemcitabine+nab-paclitaxel chemotherapy.	To further investigate the safety of the active implantable (radiological) medical device OncoSil™ when implanted intratumorally using Endoscopic Ultrasound Guidance in study participants with unresectable, locally advanced pancreatic cancer who are receiving either gemcitabine or gemcitabine+nabpaclitaxel chemotherapy.
Endpoints	**Primary Endpoints:** • AEs throughout the study • Clinical laboratory assessments (hematology and chemistry) at scheduled timepoints • Lung function at scheduled time points • Vital signs as clinically indicated • Body weight • ECG at end of study • Concomitant therapy at any time after implantation **Secondary Endpoints:** • Ease of use of ^{2}P BioSilicon™ as assessed by Investigator on Day 1 • Extent of exposure (urine/feces; whole blood; whole body [Bremsstrahlung imaging]) at scheduled time points	**Primary Endpoints:** • AEs throughout the study • Clinical laboratory assessments (hematology and chemistry) at scheduled timepoints • Lung function at scheduled time points • Vital signs as clinically indicated • Body weight • ECG at end of study • Concomitant therapy at any time after implantation **Secondary Endpoints:** • Ease of use of ^{2}P BioSilicon™ as assessed by Investigator on Day 1 • Extent of exposure (urine/feces; whole blood; whole body [Bremsstrahlung imaging]) at scheduled time points	**Primary Endpoints:** • Safety and tolerability **Secondary Endpoints:** • Local Disease Control Rate (LDCR) at 16 weeks • LDCR using best target response • Local Progression Free Survival (LPFS) within the pancreas • Progression Free Survival (PFS), all sites • Overall Survival (OS) • Body Weight • Impaired Function (Karnofsky performance status) • Pain Scores • Disease control rate (DCR) • Overall response rate (ORR) • CA 19-9 response • Quality of life (EORTC QLQ-PAN26 and EORTC QLQ-C30) • Surgical resection	**Primary Endpoints:** • Safety and tolerability **Secondary Endpoints:** • Local Progression Free Survival (LPFS), within the pancreas • Progression Free Survival (PFS), all sites • Overall Survival (OS) • Body weight • Impaired Function • Pain Scores

	• Target tumor response at study completion and scheduled time points • Non-target tumor response • Duration of target tumor response • Tumor marker assessment (CA 19-9) • BPI (Brief Pain Inventory) pain scores at scheduled time points • ECOG (Eastern Cooperative Oncology Group) performance status at scheduled time points • Progression free survival (continuing after database lock) • Overall survival (continuing after database lock)	• Target tumor response at study completion and scheduled time points • Duration of target tumor response • Tumor marker assessment (CA 19-9) • BPI pain scores at scheduled time points • ECOG performance status at scheduled time points • Progression free survival (continuing after database lock) • Overall survival (continuing after database lock)		
Number of Patients	17	6	50 by ITT; 42 by PP	9
Disease	6 LAPC; 11 mPDAC	4 LAPC; 2 mPDAC	LAPC	LAPC
Chemotherapy regimen	Gemcitabine	Gemcitabine	Gemcitabine + nab-paclitaxel or FOLFIRINOX	Gemcitabine + nab-paclitaxel
OncoSil™ planned dose to tumor	100 Gy	200 or 400 Gy	100 Gy	100 Gy
Implantation timeframe	September 2006 to January 2008	July 2006 to February 2009	April 2017 to July 2018	March 2018 to January 2019
Study location	UK and Singapore	UK	Australia, Belgium, UK	US
Inclusion Criteria	1. Histologically or cytologically proven locally advanced or metastatic adenocarcinoma of the pancreas 2. Advanced pancreatic cancer, not amenable to surgical resection 3. Measurable disease by CT scan, with a tumor burden equivalent to a diameter of no less than 2 cm, and no greater than 6 cm 4. ECOG Performance status 0-2 5. Life expectancy of at least three months 6. Laboratory parameters: • Hemoglobin (Hb) > 10 g/dl • Platelets > 100,000 mm3 • Absolute Neutrophil Count (ANC) > 1500/mm^3		1. Histologically or cytologically proven adenocarcinoma of the pancreas. 2. [OncoPaC-1: Stage III] Unresectable locally advanced pancreatic carcinoma. Patients with technically resectable tumors (T1-T3) will also be eligible, if they are deemed unresectable due to medical comorbidities or refusal of surgery. 3. Pancreatic target tumor diameter of ≥ 2.0 cm (shortest axis) to ≤ 6.0 cm (longest axis), as qualified by the central reading center. 4. An ECOG Performance Status of 0 to 1 and Karnofsky Performance Status of 80 – 100. 5. Study participants ≥ 18 years of age at screening.	

	• Bilirubin < 1.5 x upper limit of normal (ULN) • Alkaline phosphatase (AP) < 5 x ULN • Transaminases < 5 x ULN • Creatinine < 1.5 x ULN • Prothrombin (PT) and partial thromboplastin time (PTT) within normal range • Serum calcium within normal range. 7. All patients of reproductive potential must agree to use an effective barrier method of contraception during the study and for six months following termination of treatment 8. Male or female patients aged 18 or over who have provided written informed consent.	6. To commence first-line standard [PanCO: FOLFIRINOX or] gemcitabine + nab-paclitaxel chemotherapy (per standard of care according to the approved prescribing schedule), within 14 days post enrollment, with OncoSil™ implantation to occur during the fourth (4th) week of the first chemotherapy cycle. 7. Provide signed Informed Consent. 8. Willing and able to complete study procedures within the study timelines. 9. Adequate renal function: serum creatinine less than 1.5 x upper limit of normal (ULN). 10. Adequate liver function: serum liver transaminases ≤ 3 × ULN and serum bilirubin ≤ 1.5 × ULN*. *For study participants with recent biliary obstruction treated by drainage (e.g. stent), serum bilirubin of > 1.5 x ULN will be accepted for study entry provided that serial levels demonstrate clear improvement. In addition, chemotherapy should not be commenced until serum bilirubin is ≤ 1.5 × ULN. 11. Adequate bone marrow function: white blood cells (WBCs) ≥ 3,000/mm3, absolute neutrophil count (ANC) ≥ 1,500/mm3, hemoglobin ≥ 9 g/dL, and platelets ≥ 100,000/mm3. 12. Life expectancy of at least 3 months at the time of screening as judged by the investigator. 13. Treated with or eligible to commence prophylactic treatment with a proton-pump inhibitor prior to implantation, and to continue to receive treatment for at least 6 months post implantation. 14. Not pregnant, and if of childbearing potential, agrees to use adequate birth control (hormonal or barrier method of birth control or abstinence) prior to study entry and during the study and agrees not to donate sperm or ova, for the duration of the study and 12 months post implantation of the investigational device.
Exclusion criteria	1. Any previous treatment with ^{32}Phosphorus or with ^{32}P BioSilicon™ 2. Any prior radiotherapy or chemotherapy for pancreatic cancer 3. Use of other investigational agent at the time of enrolment, or within 30 days or five half-lives of enrolment, whichever is longer 4. History of hypersensitivity to any of the study products or to products with similar chemical structures (i.e. silicon or phosphorous) 5. History of malignancy of any other organ system, treated or untreated, within the past five years whether or not there is evidence of local recurrence or metastases, with the exception	1. Evidence of distant metastases, based on review of baseline CT scan, as determined by the central reading center. 2. More than one primary lesion. 3. Any prior radiotherapy or chemotherapy for pancreatic cancer. 4. Use of other investigational agent at the time of screening, or within 30 days or five half-lives of Screening Visit 1, whichever is longer. 5. Pregnant or lactating. 6. In the opinion of the investigator, EUS directed implantation posing undue study participant risk. This includes: • where previous EUS-FNA was considered technically too difficult to perform;

	of localized basal cell carcinoma of the skin and in situ cervical carcinoma 6. Pregnant or lactating women 7. Significant tumor related pain for which analgesic intervention incorporating epidural or EUS is planned.	• imaging demonstrates multiple collateral vessels surrounding or adjacent to the target tumor within the pancreas; • presence (or significant risk) of varices near to the target tumor. Note: The feasibility of implantation of the target tumor and assessment of risk can be conducted at any time between Screening Visit 1 and the implantation date. A study participant was considered for withdrawal prior to and including at the time of OncoSil™ treatment, if any of the above risk features become apparent following subject screening and/or enrollment. 7. History of malignancy, treated or untreated, within the past five years whether or not there is evidence of local recurrence or metastases, with the exception of basal cell carcinoma of the skin and cervical carcinoma in situ. 8. Evidence of radiographic invasion into stomach, duodenum or peritoneum (if not certain confirmation must be obtained prior to enrollment). 9. A known allergy or history of hypersensitivity to silicon, phosphorous or any of the OncoSil™ components. 10. Any other health condition that would preclude participation in the study in the judgment of the investigator.

Abbreviations: CCRT, chemoradiotherapy (external beam radiation therapy with concurrent chemotherapy); chemo, chemotherapy; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; Gy, Gray; ITT, intention to treat; LAPC, locally advanced pancreatic cancer; LDCR16 weeks, local disease control rate at 16 weeks; mPDAC, metastatic pancreatic ductal adenocarcinoma; PP, per protocol.

Table 4. Real World Evidence Study Summary

Study Name	**RAH/NZ**	**OSPREY Registry**
Design	RWE: retrospective 2-center study plus Propensity Score Weighted Analysis [PSWA]	RWE: multicenter observational study
Primary Objective	To compare outcomes in patients with unresectable LAPC receiving OncoSil™ plus chemotherapy versus chemotherapy alone.	To collect the following real-world observational data and information: • Safety and tolerability of OncoSil™ within a real-life clinical setting • OncoSil™ implantation performance • Overall Survival (OS) • Target (implanted) Tumor response (local and distant) • Progression Free Survival (PFS) • Surgical resection rates and outcome • Usage of pancreas cancer-related procedures • Patient reported outcomes
Number of Patients	Propensity Score: Matched: OncoSil™ 45 vs. chemo: 45 Unmatched: OncoSil™ 45 vs. chemo: 54	Safety: 67 Efficacy: 31

Disease	LAPC	LAPC
Chemotherapy Regimen	Gemcitabine + nab-paclitaxel or FOLFIRINOX or gemcitabine	nab-paclitaxel
OncoSil™ planned dose to tumor	100 Gy	100 Gy
Implantation timeframe	August 2017 to January 2023	April 2022 to ongoing
Study location	Australia, New Zealand	EU and UK
Inclusion criteria	1. Status classified as LAPC without any metastases as per National Comprehensive Cancer Network guidelines and multidisciplinary team consensus; 2. Treatment with any induction chemotherapy with or without ^{32}P implantation; 3. ECOG performance status of 0 or 1.	1. Patients who are eligible for and undergo OncoSil™ implantation at an eligible treatment facility according to the OncoSil™ System Instructions for Use, as part of their clinical care. 2. Patients who have completed and signed the Patient Informed Consent Form for the OSPREY Patient Registry.
Exclusion criteria	-	1. Participation in an interventional clinical study (company or investigator-sponsored). 2. Use of an investigational agent at the time of enrollment. Note: The feasibility of implantation of the target tumor and assessment of risk was conducted at any time prior to the implantation date. A patient was reconsidered for treatment prior to and including at the time of OncoSil™ treatment, if any risk features become apparent following the patient's initial evaluation.

Abbreviations: chemo, chemotherapy; Gy, Gray; LAPC, locally advanced pancreatic cancer; RWE, Real-World Evidence.

B. Patient Demographics

The demographic and clinical characteristics of patients enrolled in the studies described above are presented in Table 5 and 6.

Table 5. Study Participant Demographic Summary (ITT Populations)

Characteristic		Study						
		DB2-201 (n=17) [e]	DB2-202 (Total n=6)		PanCo (n=50)	OncoPaC-1 (n=9)	RAH/NZ	
			200 Gy (n=3)	400 Gy (n=3)			OncoSil™ + Chemotherapy (n=50)	Chemotherapy Only (n=54)
Age, years	Median (Range)	64 (51-91)	60 (60-79)	70 (58-76)	65 (42–84)	71 (57–87)	68.9 [f]	66.2 [f]
Sex, n (%)	Male	13 (76.5%)	3 (100%)	3 (100%)	28 (56.0%)	5 (55.6%)	32 (64.0%)	30 (55.6%)
	Female	4 (23.5%)	0 (0%)	0 (0%)	22 (44.0%)	4 (44.4%)	18 (36.0%)	24 (44.4%)
Race, n (%)	White/Caucasian	10 (58.5%)	3 (100%)	3 (100%)	40 (80.0%)	9 (100%)	-	-
	Black/African American	1 (5.9%)	0 (0%)	0 (0%)	3 (6.0%)	0 (0%)	-	-
	Asian	6 (35.3%)	0 (0%)	0 (0%)	7 (14.0%)	0 (0%)	-	-
Ethnicity, n (%)	Non-Hispanic or Latino	-	-	-	50 (100%)	9 (100%)	-	-
Screening ECOG Performance Status, n (%)	0	5 (29.4%)	1 (33.3%)	3 (100%)	26 (52.0%)	4 (44.4%)	-	-
	1	8 (47.1%)	2 (66.7%)	0 (0%)	24 (48.0%)	5 (55.6%)	-	-
	2	1 (5.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-	-
	3 [d]	1 (5.9%) [d]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-	-
Charlson Comorbidity Index score	Median (IQR)	-	-	-	-	-	5 (4-6)	5 (5-5)
Time from Enrollment to Implantation, days	Median (Range)	-	-	-	36 (25–78) [a]	35 (18–42)	-	-
Time from Chemotherapy Start to Implantation, days	Median (Range)	-	-	-	31 (21–77) [a]	32 (18–42)	-	-
Tumor Position, n (%)	Head	-	-	-	42 (84.0%)	4 (44.4%)	29 (58.0%) [h]	33 (61.1%) [h]
	Body	-	-	-	8 (16.0%)	5 (55.6%)	-	-
Target Tumor Volume, cc	Median (Range)	-	-	-	24.35 (7.9–68.7)	27.3 (8.4–52.5)	-	-
Tumor Longest Diameter, cm	Median (Range)	-	-	-	4.5 (2.6–7.1)	4.9 (3.5–6.2)	30.5 (13 [g])	26.5 (14 [g])
Extent of Pancreatic Cancer	Locally Advanced	6 (35.3%)	2 (66.7%)	2 (66.7%)	-	-	-	-
	Metastatic	11 (64.7%)	1 (33.3%)	1 (33.3%)				
Cancer Antigen 19-9 (CA 19-9), IU/mL	Median (Range)	620.5 (14-24655)	4297 (1-8593) [c]	1726 (215-4479)	163 (1–6576) [b]	357.5 (10–12000)	196 (527.5 [g])	246.5 (1238.3 [g])

[a] for implanted patients (n = 42); [b] for patients with a baseline CA 19-9 assessment (n = 49); [c] data unavailable for one patient (n=2); [d] ECOG Performance Status between 0-2 was specified as an inclusion criterion for DB2-201. The patient with an ECOG score of 3 represented a protocol violation; [e] ECOG Performance Status values only available for 15 of 17 patients; [f] Mean values; [g] Interquartile range (IQR); [h] Head/neck.

Table 6. OSPREY Registry Participant Demographic Summary

Characteristic		Chemotherapy Line and Cohort (timing of implantation relative to start of chemotherapy line)					
		1st-Line Chemotherapy			2nd-Line Chemotherapy		3rd-Line Chemotherapy
		≤ 4 Months	4-12 Months	≥ 12 Months	≤ 4 Months	4-12 Months	≤ 4 Months
Number of Patients		25	22	1	11	3	1
Age, years	Median (Range)	67 (49-84)	69.5 (47-78)	68	57 (46-79)	65 (56-66)	54
Sex, n (%)	Male : Female	10 (40.0) : 15 (60.0)	11 (50.0) : 11 (50.0)	1 (100) : 0 (0)	9 (81.8) : 2 (18.2)	1 (33.3) : 2 (66.7)	0 (0) : 1 (100)
Ethnicity	Hispanic : Non-Hispanic	14 (56.0) : 11 (44.0)	11 (50.0) : 11 (50.0)	0 (0) : 1 (100)	8 (80.0) : 2 (20.0)	3 (100) : 0 (0)	nr
ECOG Performance Status, n (%)	0	18 (72.0)	13 (61.9)	-	9 (81.8)	2 (66.7)	1 (100)
	1	7 (28.0)	8 (38.1)	1 (100)	2 (18.2)	1 (33.3)	-
Tumor Position, n (%)	Head	19 (76.0)	15 (68.2)	1 (100)	7 (63.6)	1 (33.3)	1 (100)
	Body	6 (24.0)	7 (31.8)	-	4 (36.4)	2 (66.7)	-
Tumor Longest Diameter [a], mm	Median (Range)	33 (13-61)	30 (17-60)	45	37 (13-67)	65 (45-68)	30
Tumor Volume [a], cc	Median (Range)	16.6 (3.2-93.2)	12.65 (2.3-87)	42.5	12.2 (1.8-92)	9 (4-31.1)	13.1
Time: Diagnosis to Chemo Start, months	Median (Range)	1.1 (0.0–4.0)	1.0 (0.0–3.8)	1.3	6.5 (2.9–14.1)	nc	18.7
Time: Chemo Start to Implantation, months	Median (Range)	2.6 (0.7–3.9)	6.4 (4.2–10.8)	27.3	1.6 (0.0–3.7)	9.0 (4.8–10.4)	0.4
OncoSil™ ^{32}P Activity Implanted, MBq	Median (Range)	8.7 (2–53.7)	6.9 (1.5–46.5)	25.8	7 (1.8–48)	5.7 (2.4–19)	7.3
Chemotherapy regimen, n (%)	gemcitabine + nab-paclitaxel	20 (80.0)	17 (77.3)	-	9 (81.8)	2 (66.7)	-
	PAX-gem	1 (4.0)	1 (4.5)	-	-	-	-
	gemcitabine only	3 (12.0)	3 (13.6)	1 (100)	2 (18.2)	-	1 (100)
	no concurrent chemotherapy [b]	1 (4.0)	1 (4.5)	-	-	1 (33.3)	-

[a] tumor longest diameter or volume at baseline, defined as the CT imaging assessment prior to implantation; [b] no concurrent chemotherapy, defined as no agents administered for > 3 weeks prior to OncoSil™ implantation (range 3.6 to 16.9 weeks) and none >6 weeks post-implantation (range 6.6 to 22.9 weeks).
Abbreviations: chemo, chemotherapy; nc, non-calculable; nr, not reported; PAX-gem: regimen comprises gemcitabine + nab-paclitaxel + cisplatin + capecitabine.

C. Safety Analysis

The primary safety analysis of OncoSil™ is based on the PanCO and OncoPaC-1 prospective clinical studies.

Since OncoSil™ is used in combination with systemic therapies, differentiating toxicities due to the device and chemotherapy is relevant to the assessment of safety. An analysis of the Treatment-Emergent Adverse Events (TEAEs) experienced by patients receiving OncoSil™ indicates that the majority of TEAEs were attributed by investigators as being possibly or probably related to chemotherapy (Table 7).

Table 7: Summary of Treatment-Emergent Adverse Events in the PanCO and OncoPaC-1 Studies

	PanCO + OncoPaC-1: OncoSil™ + Chemotherapy (PP: n=51)	
Category	**All Grade**	**Grade ≥3**
Total AEs/SAEs, n: all events	**1187 (100%)**	**185 (100%)**
attributed to OncoSil™ or implantation procedure only (not attributed to chemotherapy)	19 (1.6%)	4 (2.2%)
attributed to OncoSil™ and/or implantation and chemotherapy	41 (3.5%)	11 (5.9%)
Total # of Adverse Events attributed to OncoSil™ only or OncoSil™/chemotherapy	**60 (5.1%)**	**15 (8.1%)**
attributed to chemotherapy only (not attributed to OncoSil™ or implantation)	713 (60.1%)	85 (45.9%)
not attributed to either OncoSil™, implantation procedure or chemotherapy	414 (34.9%)	85 (45.9%)
Participants with ≥1 AE/SAE, n (%)	**51 (100%)**	**43 (84.3%)**
attributed to OncoSil™ or implantation procedure only (not attributed to chemotherapy)	9 (17.6%)	3 (5.9%)
attributed to OncoSil™ and/or implantation and chemotherapy	18 (35.3%)	5 (9.8%)
attributed to chemotherapy only (not attributed to OncoSil™ or implantation)	51 (100%)	36 (70.6%)
not attributed to either OncoSil™, implantation procedure or chemotherapy	45 (88.2%)	24 (47.1%)

Abbreviations and Key: AEs, adverse events; PP, per protocol; SAEs, serious AEs.

Table 8 provides the frequency of TEAEs by system organ class and preferred term which were attributed to OncoSil™ or the implant procedure and/or chemotherapy versus those events which were attributed to chemotherapy alone. There were no treatment-related Grade 5 TEAEs. The most common Grade ≥3 AEs were gastrointestinal (diarrhea, nausea), hematological (neutropenia and anemia) and fatigue, the majority of which were considered related to chemotherapy by the

treating clinician. Of the 60 adverse events reported for OncoSil™ and chemotherapy, 19 (31.7%) were solely attributed to OncoSil™. Of the 15 Grade ≥3 events reported for OncoSil™ and chemotherapy, 4 (26.7%) were attributed to OncoSil™. The overall frequencies of TEAEs across all system organ classes were consistent with that expected for unresectable LAPC patients and there were no unexpected safety signals observed. The most frequently reported OncoSil™- or procedure-related adverse events included fatigue (13.7%), abdominal pain and/or discomfort (7.8%), procedural-related pain/discomfort (7.8%) and nausea (5.9%). These events were expected for the radiation delivered by OncoSil™ and the endoscopic procedure, were transitory, conservatively managed and resolved without any clinical sequelae.

Table 8: Treatment-Emergent AEs (TEAEs/TESAEs): Incidence Overall and Causality Attributed Attributable to OncoSil™/Implantation or Chemotherapy

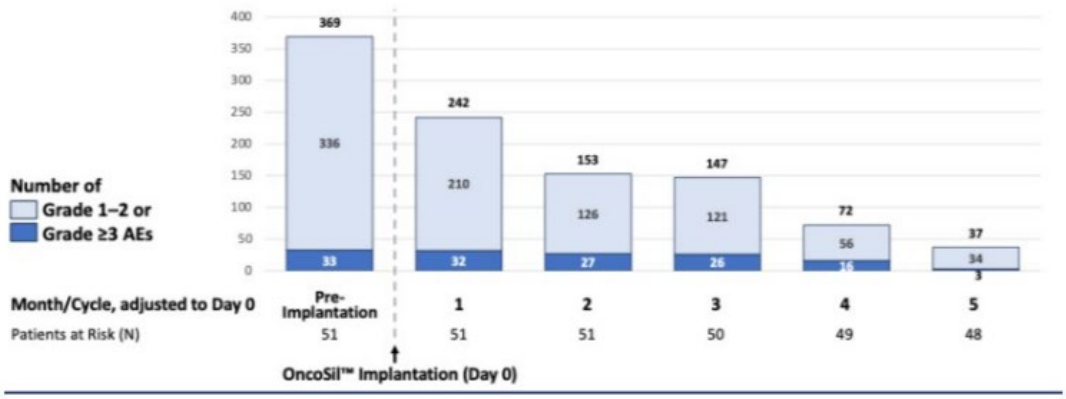
Study	Pooled Analysis of TEAEs: PanCO/OncoPaC-1 Studies					
TEAEs in ≥10% of Study Participants Overall or with Any Causality (Possibly or Probably) Attributed to OncoSil™ and/or implantation procedure	**TEAEs Irrespective of Causality: PP Population; Chemotherapy + OncoSil™** (n=51)		**Causality (Possibly or Probably) Attributed to:**			
			OncoSil™ or implant procedure only and OncoSil™/ chemotherapy (n=51) †		**Chemotherapy only** (n=51; GNP=43; FFX=8)	
TEAE/TESAE Category, n (%)	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Total Events, n	**1187**	**185**	**60**	**15**	**754**	**96**
Participants with ≥1 TEAE/TESAE	**51 (100%)**	**43 (84.3%)**	**22 (43.1%)**	**5 (9.8%)**	**51 (100%)**	**36 (70.6%)**
Gastrointestinal signs & symptoms	**50 (98.0%)**	**17 (33.3%)**	**11 (21.6%)**	**2 (3.9%)**	**42 (82.4%)**	**8 (15.7%)**
Diarrhea	30 (58.8%)	2 (3.9%)	1 (2.0%)	1 (2.0%)	22 (43.1%)	2 (3.9%)
Nausea	30 (58.8%)	3 (5.9%)	3 (5.9%)	-	26 (51.0%)	2 (3.9%)
Abdominal pain *	26 (51.0%)	6 (11.8%)	3 (5.9%)	1 (2.0%)	6 (11.8%)	1 (2.0%)
Constipation	22 (43.1%)	1 (2.0%)	-	-	10 (19.6%)	-
Vomiting	14 (27.5%)	3 (5.9%)	-	-	10 (19.6%)	1 (2.0%)
Ascites	5 (9.8%)	2 (3.9%)	-	-	1 (2.0%)	1 (2.0%)
Dry mouth	4 (7.8%)	-	-	-	4 (7.8%)	-
Abdominal distension	2 (3.9%)	-	1 (2.0%)	-	1 (2.0%)	-
Dyspepsia	3 (5.9%)	-	2 (3.9%)	-	3 (5.9%)	-
Reflux gastritis	2 (3.9%)	-	1 (2.0%)	-	1 (2.0%)	-
Stomatitis	5 (9.8%)	-	1 (2.0%)	-	4 (7.8%)	-
Dysphagia	1 (2.0%)	-	1 (2.0%)	-	1 (2.0%)	-
General disorders	**49 (96.1%)**	**12 (23.5%)**	**7 (13.7%)**	**1 (2.0%)**	**44 (86.3%)**	**8 (15.7%)**
Fatigue	40 (78.4%)	6 (11.8%)	7 (13.7%)	1 (2.0%)	38 (74.5%)	5 (9.8%)
Pyrexia	20 (39.2%)	3 (5.9%)	-	-	14 (27.5%)	2 (3.9%)
Peripheral edema *	11 (21.6%)	-	-	-	9 (17.6%)	-
Pain	6 (11.8%)	2 (3.9%)	-	-	1 (2.0%)	-
Mucosal inflammation	7 (13.7%)	1 (2.0%)	-	-	7 (13.7%)	1 (2.0%)
Blood & lymphatic system disorders *	**34 (66.7%)**	**25 (49.0%)**	**4 (5.9%)**	**1 (2.0%)**	**31 (60.8%)**	**20 (39.2%)**
Neutropenia *, comprised of:	29 (56.9%)	23 (45.1%)	5 (9.8%)	3 (5.9%)	27 (52.9%)	21 (41.2%)
Neutropenia (alone)	21 (41.2%)	14 (27.5%)	2 (3.9%)	-	19 (37.3%)	12 (23.5%)
Neutrophil count decreased	6 (11.8%)	6 (11.8%)	2 (3.9%)	2 (3.9%)	6 (11.8%)	6 (11.8%)
Febrile neutropenia	3 (5.9%)	2 (3.9%)	-	-	3 (5.9%)	2 (3.9%)
Neutropenic sepsis	2 (3.9%)	2 (3.9%)	1 (2.0%)	1 (2.0%)	2 (3.9%)	2 (3.9%)
Neutropenic colitis	1 (2.0%)	1 (2.0%)	-	-	1 (2.0%)	1 (2.0%)
Thrombocytopenia *	21 (41.2%)	5 (9.8%)	2 (3.9%)	1 (2.0%)	19 (37.3%)	3 (5.9%)
Anemia *	19 (37.3%)	11 (21.6%)	1 (2.0%)	-	16 (31.4%)	8 (15.7%)
Skin & subcutaneous tissue disorders	**40 (78.4%)**	**0 (0.0%)**	**1 (2.0%)**	**0 (0.0%)**	**36 (70.6%)**	**0 (0.0%)**
Alopecia	19 (37.3%)	-	-	-	19 (37.3%)	-
Rash	15 (29.4%)	-	-	-	15 (29.4%)	-
Pruritus	9 (17.6%)	-	1 (2.0%)	-	7 (13.7%)	-
Metabolism & nutrition disorders	**34 (66.7%)**	**10 (19.6%)**	**3 (5.9%)**	**3 (5.9%)**	**28 (54.9%)**	**4 (5.9%)**
Decreased appetite	21 (41.2%)	2 (3.9%)	-	-	19 (37.3%)	-
Hypokalemia *	11 (21.6%)	3 (5.9%)	2 (3.9%)	2 (3.9%)	6 (11.8%)	1 (2.0%)
Hypomagnesemia	6 (11.8%)	-	-	-	5 (9.8%)	-
Hypoalbuminemia	5 (9.8%)	3 (5.9%)	1 (2.0%)	1 (2.0%)	3 (5.9%)	2 (3.9%)
Hyperglycemia	5 (9.8%)	-	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)
Hyponatremia	3 (5.9%)	1 (2.0%)	-	-	2 (3.9%)	1 (2.0%)
Nervous system disorders	**30 (58.8%)**	**3 (5.9%)**	**0 (0.0%)**	**0 (0.0%)**	**26 (51.0%)**	**2 (3.9%)**
Peripheral neuropathy *	17 (33.3%)	1 (2.0%)	-	-	17 (33.3%)	1 (2.0%)
Dysgeusia	7 (13.7%)	-	-	-	7 (13.7%)	-

Paresthesia	6 (11.8%)	-	-	-	4 (7.8%)	-
Dizziness	6 (11.8%)	-	-	-	2 (3.9%)	-
Respiratory disorders NEC	**24 (47.1%)**	**5 (9.8%)**	**3 (5.9%)**	**1 (2.0%)**	**16 (31.4%)**	**2 (3.9%)**
Pulmonary embolism	6 (11.8%)	5 (9.8%)	1 (2.0%)	1 (2.0%)	3 (5.9%)	1 (2.0%)
Dyspnea	8 (15.7%)	-	-	-	2 (3.9%)	-
Epistaxis	5 (9.8%)	1 (2.0%)	-	-	4 (7.8%)	-
Dysphonia	1 (2.0%)	-	1 (2.0%)	-	-	-
Oropharyngeal pain	6 (11.8%)	-	2 (3.9%)	-	2 (3.9%)	-
Hiccups	4 (7.8%)	1 (2.0%)	-	-	2 (3.9%)	-
Nasal congestion	3 (5.9%)	-	-	-	1 (2.0%)	-
Investigations *	**29 (56.9%)**	**16 (31.4%)**	**5 (9.8%)**	**2 (3.9%)**	**25 (49.0%)**	**13 (25.5%)**
Weight decreased	17 (33.3%)	3 (5.9%)	2 (3.9%)	-	13 (25.5%)	1 (2.0%)
Platelet count decreased [*also included above*] *	10 (19.6%)	2 (3.9%)	1 (2.0%)	-	9 (17.6%)	2 (3.9%)
White blood cell count decreased	6 (11.8%)	4 (7.8%)	1 (2.0%)	-	6 (11.8%)	3 (5.9%)
Neutrophil count dec. [*also included above*] *	6 (11.8%)	6 (11.8%)	2 (3.9%)	2 (3.9%)	6 (11.8%)	6 (11.8%)
Blood alkaline phosphatase increased	4 (7.8%)	1 (2.0%)	-	-	2 (3.9%)	1 (2.0%)
Aspartate aminotransferase increased	3 (5.9%)	-	-	-	2 (3.9%)	-
Lymphocyte count decreased	2 (3.9%)	2 (3.9%)	1 (2.0%)	1 (2.0%)	3 (5.9%)	2 (3.9%)
Hemoglobin decreased [*also included above*] *	2 (3.9%)	1 (2.0%)	-	-	1 (2.0%)	-
Neutrophil count increased	1 (2.0%)	-	1 (2.0%)	-	1 (2.0%)	-
Prothrombin time prolonged *	1 (2.0%)	-	1 (2.0%)	-	1 (2.0%)	-
Infections & infestations	**35 (68.6%)**	**12 (23.5%)**	**1 (2.0%)**	**1 (2.0%)**	**20 (39.2%)**	**3 (5.9%)**
Cellulitis	7 (13.7%)	1 (2.0%)	-	-	5 (9.8%)	-
Oral candidiasis	5 (9.8%)	-	-	-	4 (7.8%)	-
Neutropenic sepsis [*also included above*] *	2 (3.9%)	2 (3.9%)	1 (2.0%)	1 (2.0%)	2 (3.9%)	2 (3.9%)
Vascular disorders	**15 (29.4%)**	**4 (7.8%)**	**1 (2.0%)**	**0 (0.0%)**	**5 (9.8%)**	**0 (0.0%)**
Hypotension	7 (13.7%)	-	1 (2.0%)	-	1 (2.0%)	-
Injury, poisoning & procedural complications	**11 (21.6%)**	**8 (15.7%)**	**1 (2.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Venous intravasation	1 (2.0%)	-	1 (2.0%)	-	-	-
Cardiac disorders	**6 (11.8%)**	**-**	**1 (2.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Tachycardia	6 (11.8%)	-	1 (2.0%)	-	-	-
Musculoskeletal & connective tissue	**16 (31.4%)**	**1 (2.0%)**	**0 (0.0%)**	**0 (0.0%)**	**9 (17.6%)**	**0 (0.0%)**
Back pain	7 (13.7%)	1 (2.0%)	-	-	-	-
Product issues	**6 (11.8%)**	**4 (7.8%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Device occlusion	6 (11.8%)	4 (7.8%)	-	-	-	-
Total non-hematological events	**51 (100%)**	**39 (76.5%)**	**20 (39.2%)**	**4 (5.9%)**	**51 (100%)**	**28 (54.9%)**

Abbreviations: AE, adverse event; dec., decreased; FFX, FOLFIRINOX; GNP, gemcitabine + nab-paclitaxel; ITT, intention-to-treat (enrolled participants); PP, per protocol (enrolled and implanted participants); SAE, serious adverse event; TE, treatment-emergent; -, no TEAEs/TESAEs.

Notes: Multiple records from the same study participants are only counted once within the same category. † includes TEAEs also attributed to chemotherapy; *, Combined records: Abdominal pain includes TEAEs reported as abdominal pain irrespective of abdominal site of pain (lower, upper or not otherwise specified); Peripheral oedema includes TEAEs reported as oedema peripheral and/or peripheral swelling; Neutropenia includes TEAEs reported as neutropenia, febrile neutropenia, neutropenic colitis, neutropenic sepsis and/or neutrophil count decreased; Thrombocytopenia includes TEAEs reported as thrombocytopenia and/or platelet count decreased; Anemia includes TEAEs reported as anemia and/or hemoglobin decreased; Hypokalemia includes TEAEs reported as hypokalemia and/or blood potassium decreased; Peripheral neuropathy includes TEAEs reported as peripheral neuropathy and/or peripheral sensory neuropathy; Prothrombin time prolonged includes TEAEs reported as prothrombin time prolonged and/or increased international normalized ratio (INR).

The frequency of AEs was analyzed and showed a decrease over time (up to 5 months) following OncoSil™ implantation (Figure 1).



Abbreviations: AE, adverse event; Note: FOLFIRINOX chemotherapy cycles were adjusted (i.e. two 14-day cycles are combined to give equivalent timespan as a 28-day cycle of gemcitabine + nab-paclitaxel). 8 of the 51 study participants in the PP cohort received 2 cycles of chemotherapy prior to OncoSil™ implantation

Figure 1: Incidence of Overall, Grade 1–2 and Grade ≥3 AEs/SAEs Pre- and Post-Implantation by Monthly Chemotherapy Cycle in PanCO and OncoPaC-1 Study Participants that were Alive (PP Population), Adjusted to Date of OncoSil™ Implantation.

To further evaluate the safety of OncoSil™ when used in conjunction with chemotherapy, the overall frequency of selected Grade ≥ 3 adverse in LAPC patients treated in the PanCO and OncoPaC-1 studies were compared to results of pivotal Phase III randomized controlled trial (RCTs) of FOLFIRINOX and gemcitabine + nab-paclitaxel that established the standard of care for pancreatic cancer (Table 9). This analysis shows that the AE profile of OncoSil™ + chemotherapy is comparable to chemotherapy alone.

Table 9: Adverse Events in Patients Implanted with OncoSil™ + Chemotherapy, Compared with Pivotal Phase III RCTs in Pancreatic Cancer using the Same Chemotherapy Regimens Alone

Safety Measure		**PanCO and OncoPaC-1 Studies (OncoSil™ + Chemotherapy) (N = 51)**	**Pivotal Pancreatic Cancer Phase III RCTs (Chemotherapy Alone) [d] (N = 171 + 421)**
AE leading to death	%	0%	0.6 – 4.3%
Hematological AEs (Any Causality)			
Neutropenia	Grade 3+, %	41.2% [a]	37.8 – 45.7%
Febrile neutropenia	Grade 3+, %	3.9% [a]	3.5 – 5.4%
Leukopenia	Grade 3+, %	9.8% [b]	30.6%
Thrombocytopenia	Grade 3+, %	9.8%	9.1 – 12.8%
Anemia	Grade 3+, %	21.6%	7.8 –13.1%
Non-Hematological AEs (Any Causality)			

Fatigue	Grade 3+, %	11.7%	17.3 – 23.6%
Peripheral neuropathy	Grade 3+, %	2.0%	9.0 – 17.3%
Diarrhea	Grade 3+, %	3.9%	5.9 – 12.7%
Vomiting	Grade 3+, %	5.9%	14.5%
Elevated level of alanine aminotransferase	Grade 3+, %	2.0%	7.3%
Thromboembolism	Grade 3+, %	0% [c]	6.6%

Abbreviations and Key: AEs, adverse events; [a] rates for neutropenia include neutrophil count decreased, neutropenic sepsis and neutropenic colitis (febrile neutropenia is shown separately); [b] leukopenia or white blood cell count decreased; [c] in PanCO and OncoPaC-1, 9.8% patients had pulmonary embolism; [d] Conroy, et al. (N Engl J Med 2011; 364: 1817–25. doi: 10.1056/NEJMoa1011923) and Von Hoff, et al. (N Engl J Med 2013; 369(18): 1691–703. doi: 10.1056/NEJMoa1304369)

Gastrointestinal TEAEs:
The occurrence of some gastrointestinal (GI) TEAEs were anticipated due to either OncoSil™ implantation or endoscopy procedure-related risks (e.g., abdominal pain, abdominal distension, diarrhea, nausea, vomiting, dyspepsia, dysphagia, reflux gastritis, stomatitis). However, GI TEAEs reported in the PanCO and OncoPaC-1 studies were also analyzed in order to identify any potential unanticipated GI TEAEs.

Some GI TEAEs observed in the PanCO and OncoPaC-1 studies included duodenal obstruction, duodenitis, epigastric discomfort, gastric obstruction, and upper gastrointestinal hemorrhage. However, the causality of these GI TEAEs was not attributed to OncoSil™ and/or the implantation procedure.

All GI TEAEs were analyzed, irrespective of causality, in order to identify any association with unanticipated GI TEAEs. There was no evidence from the analysis to suggest any negative effects from OncoSil™ and/or the implantation procedure on the GI tract or any association with gastric and duodenal adverse events. The pattern of gastric and duodenal TEAEs is consistent with the natural history of patients with pancreatic cancer.

Pancreatic-, Biliary- and Stent-Associated AEs/TEAEs:
No pancreatic-, biliary- or stent-associated TEAEs were attributed to OncoSil™ or the implantation procedure in either the PanCO or OncoPaC-1 studies. The pattern of biliary and pancreatic AEs was also consistent with the natural history of patients with pancreatic cancer.

Radiation Dosimetry:
Pharmacokinetics, biodistribution, and dosimetry of OncoSil™ were evaluated in patients from the two prospective clinical studies (PanCO and OncoPac-1) to estimate whole body and normal organ absorbed doses and effective dose equivalent. Dosimetry data were obtained using post-administration bremsstrahlung-SPECT imaging (acquired for the purpose of verifying activity localization and not for quantitative imaging and dosimetry analysis) (informed by patient data from PanCO (n=42) and OncoPaC-1 (n=9)) as well as bioassay of activity in blood and urine (both informed by patient data from PanCO (n=26) and OncoPaC-1 (n=9)).

With ^{32}P primarily localizing in the clinical target volume, significant ^{32}P was not detected outside the implant site. Trace ^{32}P was detected in some patient urine samples (29 of 51 patients, nominally less than 0.5% of administered activity). A small amount of ^{32}P-microparticles was associated with the endoscope flush into the stomach (19 of 51 patients, about 0.1% of administered activity). Fecal samples collected in patients showed ^{32}P activity amounts higher than the activity measured in the blood and urine samples. This excretion of ^{32}P has been associated mainly with the catheter flush and not with the biodistribution of ^{32}P microparticles or with free ^{32}P away from the tumor site. Further, localization of the device within the tumor was confirmed with a histopathology analysis from pancreatectomy specimens from patients with locally advanced pancreatic adenocarcinoma following treatment with OncoSil™.

Absorbed dose estimates, calculated using MIRDcalc ver. 1.23 Genesis based on computed time-integrated activity coefficients from average bioassay measurement values, assumed a mean implanted OncoSil™ activity of 14.0 MBq (0.38 mCi), equivalent to the mean implanted activity in the target from the two clinical studies. Approximately 0.5% (or 0.72 MBq) ^{32}P was assumed to migrate via blood to the kidneys and urinary bladder.

Table 10 shows the calculated absorbed dose per unit administered activity (mGy/MBq) and absorbed dose for a 14 MBq infusion into the tumor. The organs with the highest radiation absorbed doses are the urinary bladder wall and colon.

Table 10: Estimated Radiation Absorbed Doses for OncoSil™

Organ/Tissue	Absorbed Dose per Unit Administered Activity (mGy/MBq)	Standard Deviation (±S.D.) (mGy/MBq)	Absorbed Dose per 14 MBq Infused (mGy)
Colon	2.64×10^{-3}	5.28×10^{-4}	3.70×10^{-2}
Kidneys	2.13×10^{-4}	4.25×10^{-5}	3.0×10^{-3}
Small intestine	7.07×10^{-4}	1.41×10^{-5}	9.90×10^{-3}
Stomach	5.21×10^{-4}	1.02×10^{-4}	7.3×10^{-3}
Urinary bladder wall	4.02×10^{-3}	8.05×10^{-4}	5.63×10^{-2}
All other organs and tissues	Less than 1.0×10^{-5}	---	Less than 1.5×10^{-4}

a) Absorbed dose estimates calculated using MIRDcalc ver. 1.23 Genesis based on computed time-integrated activity coefficients from average bioassay measurement values.

b) Calculated ICRP Effective Dose (whole body) = 5.24×10^{-4} mSv/MBq (7.34×10^{-3} per 14 MBq infused).

DB2-201, DB2-202, and RWE studies:
For DB2-201 and DB2-202, the majority of AEs were mild to moderate in severity. The most common AEs experienced were gastrointestinal disorders (e.g.,

constipation, nausea and vomiting). There were no life-threatening events, deaths or patients withdrawn due to AEs and no AEs were related to the OncoSil™ device.

For the OSPREY registry, there is no evidence of safety concerns or unexpected/serious toxicities associated with OncoSil™ in clinical practice. Limited AEs (14.9% of patients; all Grade 1–2) were attributed to OncoSil™ and/or implantation procedure, and no SAEs.

For the RAH/NZ study, no (0) acute complications and no (0) OncoSil™- or procedure-related Grade ≥3 AEs were reported.

D. Benefit Analysis

The probable benefit of OncoSil™ was primarily supported by the results of the propensity score analysis from the retrospective RAH/NZ study. This serves as the principal basis and support for the probable benefit assessment, whereas the effectiveness results from the prospective studies discussed above and a real-world patient registry (OSPREY Registry) were considered secondary/supportive.

To adjust for potential confounding factors related to treatment allocation and outcome, a propensity score matched-pair analysis was conducted for 45 unresectable LAPC patients receiving OncoSil™ + chemotherapy vs. 45 patients receiving chemotherapy (± chemoradiotherapy) only. Per Figure 2, the overall survival (OS) for the OncoSil™ + chemotherapy group was longer than that of the chemotherapy group as measured by Kaplan-Meier analysis (median OS: 19.5 *vs*. 12.2 months, respectively; $p<0.001$). This indicates a >60% reduction in mortality for patients treated with OncoSil™ + chemotherapy compared to chemotherapy alone (hazard ratio [HR] 0.38; 95% CI: 0.23–0.63, $p<0.001$). This result was corroborated by a 70% reduction in disease progression for patients receiving OncoSil™ + chemotherapy compared to chemotherapy alone (median PFS: 15.2 *vs*. 9.0 months, respectively; HR 0.31; 95% CI: 0.19–0.50, $p<0.001$). Further confirmation of local disease control was indicated by a 55% reduction in local progression for OncoSil™-treated patients compared to chemotherapy alone (HR=0.45; 95% CI: 0.27–0.74, p=0.002).

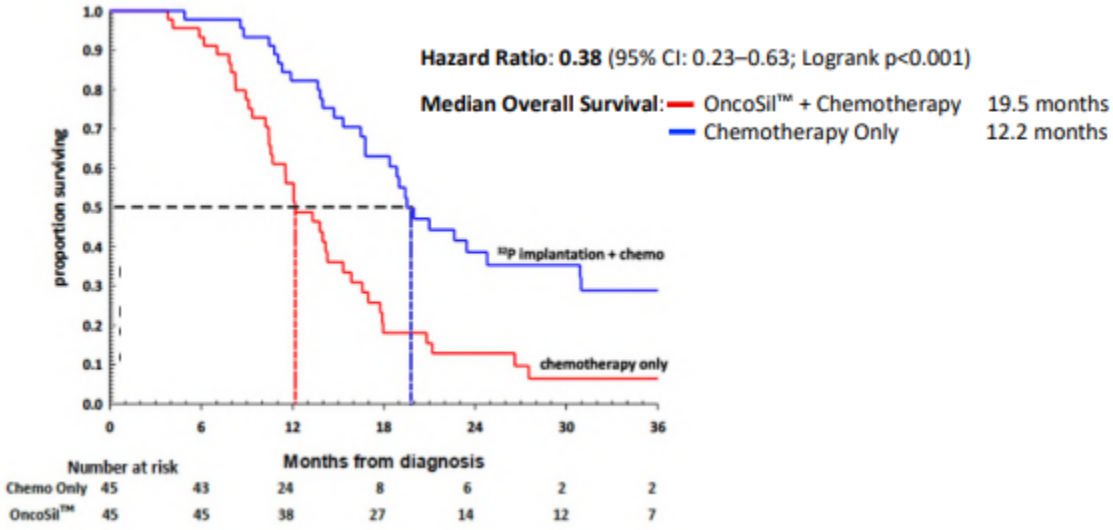


Figure 2: Kaplan-Meier Overall Survival Curves for the Propensity Score Matched Population

In addition to the primary support provided from the propensity score analysis from the retrospective RAH/NZ study, the results from the prospective studies and the OSPREY registry provide additional support for the probable benefit of OncoSil™ (Table 11). The endpoints described in this table are considered clinically relevant in unresectable dCCA, where morbidity and mortality are primarily driven by local tumor progression and biliary obstruction. Potential downstaging and conversion to resectability is also clinically meaningful given that surgery is the only potentially curative option.

Table 11: Efficacy Outcomes for OncoSil™ in Patients Presenting with LAPC in the PanCO and OncoPaC-1 Studies, RAH/NZ Propensity Score Analysis and OSPREY Registry

Efficacy Measure, (95% CI)	Prospective Studies		Real-World Evidence			
			RAH/NZ Propensity Score Analysis			OSPREY Registry
	PanCO OncoSil™ + Chemotherapy (N=42)	OncoPaC-1 OncoSil™ + Chemotherapy (N=9)	OncoSil™ + Chemotherapy (N=45)	vs. HR p-value	Chemotherapy Only (N=45)	OncoSil™ + Chemotherapy (N=31)
LDCR $_{16\ weeks}$ [a]	90.5% (77.4–97.3)	77.8%	nr		nr	90.5% [a b]
Objective Resp. Rate, %	31.0% (17.6–47.1)	22.2%	nr		nr	21.7% [b]
Downstaged, %	33.3%	nr	31.4%	p=0.03	13.6%	nr
Surgically Resected, %	23.8% (12.1–39.5)	0%	28.6%	p=0.04	12.1%	nr
Overall PFS, median (mo)	9.3 (5.8–11.3)	12.2 (3.5–nc)	15.2 (12.8–16.4)	HR 0.31 p<0.001	9.0 (6.8–9.5)	nr
Local PFS, median (mo)	9.8 (7.3–12.6)	27.3 (3.5–nc)	nr	nr	nr	nr
Local progression*	nr	nr	nr	HR 0.45 p=0.002	nr	nr
Overall Survival, median (mo)	15.5 (11.4–20.1)	27.3 (9.3–nc)	19.5 (16.8–24.8)	HR 0.38 p<0.001	12.2 (10.6–14.3)	18.0 (16.9–23.8)

Abbreviations: Downstaged, technically resectable; LDCR $_{16\ weeks}$, local disease control rate at 16 weeks from commencing chemotherapy ([a] 12 weeks post-implantation); mo, months; nc, non-calculable; nr, not reported; PFS, Progression-Free Survival; 95% CI, 95% confidence interval. [b] compared to baseline imaging immediately prior to implantation; *Distant progression/death versus local progression as the first event using competing risk analysis.

DB2-201 and DB2-202:

For DB2-201, four patients (23.5%) had partial response, fourteen patients (82%) had stable or controlled disease and two patients (11.8%) experienced disease progression. Twelve patients (70.6%) demonstrated tumor volume regression at Week 8. The median progression-free survival (PFS) was 121 days and the median overall survival (OS) was 309 days. The observed target tumor response rate (TTRR) was 23.5% (95% CI 6.8%, 49.9%), which was statistically significantly greater than the pre-determined TTRR of 5% (p=0.008).

For DB2-202, three patients completed the study as planned. Three patients did not complete the full study due to disease progression. All patients had stable disease throughout the study, there were no patients with complete or partial response.

Subgroup Analyses:

Subgroup analyses were performed for PanCO (chemotherapy regimen, timing of AEs relative to implantation of OncoSil™), and for the OSPREY Registry (baseline demographic/treatment characteristics and outcomes by line of treatment received and timing of OncoSil™ implantation relative to commencing chemotherapy). However, neither study was specifically powered for these subgroup analyses. For OncoPaC-1, there were no analyses performed for sex-, age-, race-, ethnicity-, or any other relevant characteristic-specific subgroups

Pediatric Extrapolation

In this premarket application, 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. None of the clinical investigators involved in the studies had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

A. Probable Benefit Conclusions

The assessment of probable benefit of OncoSil™ is primarily based on propensity score analysis from the retrospective RAH/NZ study, which showed a benefit in terms of overall survival (OS). The effectiveness results from the prospective studies discussed above and post-market OSPREY Registry were considered secondary/supportive. In the RAH/NZ study, to adjust for potential confounding factors related to treatment allocation and outcome, a propensity score matched-pair analysis was conducted for 45 unresectable LAPC patients receiving OncoSil™ + chemotherapy vs. 45 patients receiving chemotherapy (± chemoradiotherapy) only. The OS for the OncoSil™ + chemotherapy group was longer than that of the chemotherapy alone group as measured by Kaplan-Meier analysis (median OS: 19.5 vs. 12.2 months, respectively; $p<0.001$). This represents a >60% reduction in mortality for patients treated with OncoSil™ + chemotherapy compared to chemotherapy alone (hazard ratio [HR] 0.38; 95% CI: 0.23–0.63, $p<0.001$). This result was corroborated by a 70% reduction in disease progression for patients receiving OncoSil™ + chemotherapy compared to chemotherapy alone (median PFS: 15.2 vs. 9.0 months, respectively; HR 0.31; 95% CI: 0.19–0.50, $p<0.001$). Further confirmation of local disease control was indicated by a 55% reduction in local progression for OncoSil™-treated patients compared to chemotherapy alone (HR 0.45; 95% CI: 0.27–0.74, $p=0.002$).

B. Safety Conclusions

The primary safety analysis of OncoSil™ is based on the PanCO and OncoPaC-1 prospective clinical studies that recruited 50 and 9 patients, respectively. A combined analysis of the safety outcomes of the PanCO and OncoPaC-1 studies demonstrated that the safety profile of OncoSil™ added to chemotherapy is comparable to patients receiving multi-agent systemic chemotherapy for LAPC. The AEs attributed to OncoSil™ and/or the implantation procedure were low (60 across the 2 studies out of

a total 1187 events, or 5.1%) and anticipated. Comparably, the number of AEs attributed to chemotherapy was notably higher (754 out of a total 1187 events, or 63.5%). Analysis of gastrointestinal and pancreatic, biliary and stent-associated AEs/TEAEs did not show evidence to suggest increased or unanticipated negative effects from the OncoSil™ device and/or implantation procedure. There was no evidence of AEs (including radiation-related events) in organs of concern (e.g. gastrointestinal tract, liver, kidneys, lungs) in patients treated with OncoSil™ from the leveraged clinical studies. In addition, the SPECT imaging data along with blood, urine, and fecal analyses demonstrates the device primarily remains where injected.

C. Probable Benefit-Risk Conclusions

The safety and probable benefits of the device are based on data leveraged to support HDE approval as described above (non-clinical, clinical (prospective and retrospective), post-market registry).

A few uncertainties exist: (1) Due to the rarity of dCCA, clinical studies were collected for a different indication (locally advanced pancreatic cancer) and thus might not be fully representative of the proposed indications for use. (2) The clinical studies used OncoSil with chemotherapy, and thus it is unclear if the clinical responses/attribution were directly due to the device itself (potentially confounding), (3) the studies were single-arm (lack of concurrent comparison/control), and (4) Attribution of AEs to the device was made by investigators and it is not always clear why attribution was made to chemotherapy rather than the device, and (5) there are uncertainties with the ability of the OSPREY registry to capture probable benefit and safety because: (i) it is not a comparative study, (ii) all patients treated with OncoSil are encouraged to enroll irrespective of the extent of prior treatment or baseline characteristics, which means that the design is susceptible to selection bias and other inherent biases, (iii) there is limited information on whether patients were treated according to a consistent protocol, and (iv) it is not possible to isolate device-related benefits from those of standard-of-care treatments. It is noted that there are commonalities between dCCA and locally advanced pancreatic cancer (LAPC), and thus there could be a similar safety and efficacy profile in patients with dCCA compared to that observed in patients with LAPC, and thus, the assessments outlined herein have leveraged data from the LAPC population.

The probable benefits outweigh the risks if the appropriate mitigations are in place. With these in place, it is determined that OncoSil™ will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. OncoSil™ would not be available to a person with dCCA without the HDE, and no comparable device, other than another device approved under an HDE or IDE, is available to treat dCCA. While chemotherapy and external beam radiation therapy are alternative treatments for dCCA (and palliative care is an option), there is no comparable device available to treat dCCA. OncoSil™ has the potential to extend overall survival beyond current alternatives. Unlike an

evaluation of a device for premarket approval, which requires a finding of reasonable assurance of safety and effectiveness of a subject device, the standard for approving an HDE is different. It requires, among other things, a finding of probable benefit rather than a reasonable assurance of effectiveness. The data submitted by the sponsor for OncoSil™, when combined with the additional risk mitigations, provide a sufficient basis to grant an HDE for OncoSil™. The additional risk mitigations include: a) Clear labeling that allows patients and physicians to make informed decisions by including clear descriptions of the risks and benefits of the device, the limitations of the available information on the risks and benefits, and instructions on how to correctly administer the device; b) A post approval study (PAS) to address remaining uncertainty. A PAS will be conducted in which clinical use of the device following HDE approval will be limited to patients agreeing to take part in the PAS.

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 HDE for this device.

In conclusion, given the available information above, the data support that for the indication for use of the device in the intended dCCA population, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of OncoSil™ when used in accordance with the indications for use identified above.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not reviewed by an FDA Advisory Panel because the information in this HDE did not raise any unanticipated safety concerns. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, OncoSil™ will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury.

CDRH issued an approval order on August 14, 2026. The final clinical conditions of approval cited in the approval order are described below.

> The Post Approval Study (PAS) titled *Distal Cholangiocarcinoma Study* is a multicenter, observational, prospective study to evaluate the safety and probable benefit of OncoSil™ in patients with distal cholangiocarcinoma (dCCA) that is both unresectable (locally advanced and/or unfit for surgery) and non-metastatic, as an adjunct to systemic therapy. The study objectives include assessment of overall survival, safety and tolerability including device-, procedure-, stent-, and disease-related adverse events, OncoSil™ implantation performance, biliary patency, local disease control/progression, target tumor response, progression-free survival and local progression-free survival, and surgical resection rates and outcomes. Enrollment in the PAS will be required for clinical use of the device, ensuring OncoSil™ is used exclusively in the intended use population by appropriately trained individuals in a closely monitored setting. Enrollment will be limited to patients with locally advanced, unresectable dCCA who meet the following selection criteria, all consistent with the device's proposed indications for use: (1) biliary stricture/occlusion at the pancreatic head; (2) absence of pancreatic duct dilation; (3) normal appearing pancreas; and (4) elevated LFTs/bilirubin – jaundice. Biliary patency will be restored by stenting or other means prior to OncoSil™ administration. A total of 30 patients will be enrolled and followed every 3 months (± 2 weeks) until death or 24 months of follow-up, whichever occurs first. If 30 patients are not enrolled within the first 24 months, enrollment will continue until at least 30 patients have received OncoSil™ and completed follow-up. Until the PAS is completed, US-distribution of OncoSil™ will be limited to a maximum of 5 US-based treatment sites appropriately trained in the device's technology and administration. 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 PAS database webpage after submission of each report.

The applicant's manufacturing facility was 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 the device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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