OncoSil™ System

Instructions For Use manual

Product Name: OncoSil™

Product Number: OS01

Humanitarian Device:

Authorized by Federal law for the treatment of patients with unresectable and non-metastatic distal cholangiocarcinoma (dCCA) as an adjunct to chemotherapy. The effectiveness of this device for this use has not been demonstrated.

Caution: Federal law restricts this device to sale by or on the order of a physician.

⚠ **Please read these Instructions For Use in their entirety prior to using OncoSil™**

1. 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 single-use brachytherapy device used to deliver a planned dose of 100 Gy of beta radiation directly into a tumor via direct injection (intratumoral implantation) under ultrasound-guided endoscopy using a biopsy needle that has been advanced within the echoendoscope.

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 by combining highly pure silicon with phosphorous, to produce grey-black Microparticles.

The implantation procedure takes under an hour to perform using standard endoscopic techniques. Once implanted in the target tumor, placement of the device is confirmed within 4 hours by Single-Photon Emission Computed Tomography (SPECT-CT) Bremsstrahlung imaging. Once implanted, the OncoSil™ microparticles remain permanently in the tumor.

The Microparticles are provided in individually crimp-sealed vials, containing 250 ±10% MBq at 11:00 AM (GMT) or 6:00 AM (EST) on the reference date. Each vial is moist heat (autoclave) sterilized. Each individual vial of Microparticles is placed inside an acrylic lined lead pot to shield personnel from radiation during shipping and handling.

The Diluent comprises inactive pharmacopeia grade excipients and performs as a carrier to facilitate implantation of the Microparticles into the target treatment tumor.

The Diluent is moist heat (autoclave) sterilized and 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.

The device is MR Safe – the implanted device does not contain any metallic component.

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

2. DEVICE PRINCIPLE OF OPERATION / MODE OF ACTION

The implanted portion of OncoSil™ is intended to induce prolonged local tumor control and tumor size reduction in patients with distal cholangiocarcinoma (dCCA), in addition to standard of care chemotherapy, by implantation of radioactive Phosphorous-32 Microparticles into dCCA tumors under endoscopic ultrasound guidance.

3. INTENDED USE / INTENDED PURPOSE

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

4. 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.

5. ADVERSE EVENTS

In the previous clinical studies, the following adverse events were considered to have a possible, probable or definite causal relationship with 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

6. WARNINGS

- If any signs of damage or ineffective sterile barrier integrity are observed for the components of the OncoSil™ System, DO NOT USE the system and contact OncoSil Medical. Signs of damage and/or ineffective sterile barrier integrity may include, for example, broken vial, cracked vial, broken ring pull, non-intact tamper evident seals, missing vial caps etc.

- The implantable components of OncoSil™ are supplied sterile. There are no data to support the sterility or functionality of OncoSil™ past its expiration date.

7. 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.

8. PRECAUTIONS

- Caution is advised where previous endoscopic ultrasound (EUS) (e.g. diagnostic EUS- fine-needle aspiration (FNA)) was considered technically too difficult.
- Caution is strongly advised in the setting of recent, clinically significant pancreatitis. Implantation is not recommended.
- OncoSil™ has not been studied in patients who have previously received radiotherapy to the target organ.
- Retreatment with OncoSil™ has not been evaluated.
- Since the combination of standard radiotherapy and OncoSil™ has not been investigated, additional radiotherapy is not recommended following OncoSil™ treatment.
- Antibiotic prophylaxis to cover the OncoSil™ implantation procedure is advised. The selection and duration of antimicrobial regimen is based on local guidelines and practice.
- Pain relief may be required to treat abdominal pain experienced immediately following implantation of OncoSil™.
- Gastro-protection e.g., with a proton-pump inhibitor or similar therapy, starting just prior to or at the time of implantation, and continued for up to 6 months post-implantation is considered reasonable.
- Safety and probable benefit in patients who are pregnant or who, within twelve months of implantation, become pregnant have not been established.

- Safety and probable benefit in future children of patients who are pregnant at the time of implantation, or who, within twelve months of implantation, become pregnant have not been established.
- Safety and probable benefit in children being breastfed by patients at the time of implantation or subsequent to implantation have not been established.
- Safety and probable benefit in patients who are ≤ 21 years of age have not been established.
- Due to limited clinical experience, caution is advised when treating tumors with volumes in excess of 50cc with OncoSil™. A risk-benefit assessment by the implanting physician is strongly advised.
- Patients presenting with dCCA at initial diagnosis typically undergo biliary drainage and stent placement to relieve symptoms (jaundice, pruritus) and stabilize liver function to permit the safe delivery of systemic chemotherapy. Liver function tests following stent placement must be within normal range before OncoSil™ is administered.
- See also Section 23 – Radiation Safety Guidelines of the labeling for additional precautions related to radiation handling.

9. SERIOUS INCIDENTS

Any serious incident that has occurred in relation to OncoSil™ must be reported to OncoSil Medical IMMEDIATELY, and without delay to complaints@oncosil.com. A serious incident (Serious Adverse Event) is defined as:

- Any untoward medical occurrence(s) that at any dose results in death, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or a congenital anomaly or birth defect

10. SAFETY AND PROBABLE BENEFIT

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). Currently, there are no data on the safety or probable benefit of OncoSil™ in patients with dCCA. Given the anatomic, physiological and functional similarities of LAPC and dCCA, the data on LAPC are supportive of, and are clinically relevant to, an assessment of safety and probable benefit of OncoSil™ for the dCCA population.[1] Further, for studies of OncoSil™ in patients with LAPC, device use was combined with systemic therapy (FOLFIRINOX, gemcitabine + nab-paclitaxel, or gemcitabine).

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).

Since prospective clinical data specific to unresectable, non-metastatic dCCA are limited due to the rarity of the condition, the clinical evidence package includes data from LAPC studies in which OncoSil™ was implanted using the same EUS-guided intratumoral technique in anatomically adjacent pancreaticobiliary tumors. These data are considered relevant to the dCCA indication because they support the feasibility of EUS-guided implantation, characterize OncoSil™- and procedure-related safety, and demonstrate local tumor control following intratumoral delivery of phosphorus-32 microparticles. The limitations of extrapolating from LAPC to dCCA are addressed by the similarity of LAPC and dCCA noted above, the rarity of the HUD population, the local mechanism of action, and the supportive real-world clinical experience.

DB2-201 Study

DB2-201 was an open Label, phase IIa, safety study of the active implantable (radiological) medical device ^{32}P BioSilicon™, administered intratumourally to patients with advanced, unresectable pancreatic cancer, in addition to standard intravenous gemcitabine chemotherapy. The study recruited 17 subjects (6 LAPC; 11 metastatic PDAC) between September 2006 to January 2008 at centers in the UK and Singapore. The primary objective of the study was 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.

DB2-202 Study

DB2-202 was an open label, phase IIB, dose escalating safety study of the active implantable (radiological) medical device ^{32}P BioSilicon™, administered intratumourally to patients with advanced, unresectable pancreatic cancer, in addition to standard intravenous gemcitabine chemotherapy. The study recruited 6 patients between July 2006 to February 2009 in the UK. The primary objective was 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. 3 patients were assigned to each planned dose (either 200 Gy or 400 Gy).

PanCO Study

PanCO was a company-sponsored, open-label, single-arm study of OncoSil™ in study participants with unresectable locally advanced pancreatic cancer (LAPC) who received either FOLFIRINOX or gemcitabine + nab-paclitaxel chemotherapy.[2] The study recruited 50 participants (of which 42 received OncoSil™) between March 2017 and June 2018 across 10 centers in Australia, Belgium and the UK. The primary objective of the study was to evaluate the safety/tolerability of OncoSil™ when added to contemporary systemic chemotherapy regimens, and the feasibility of the device and EUS-directed implantation. In addition, the study evaluated the clinical performance of OncoSil™, including the primary efficacy endpoint of target tumor local disease control rate at 16 weeks ($LDCR_{16\ weeks}$).

OncoPaC-1 Study

OncoPaC-1 was a company-sponsored, open-label, single-arm study of OncoSil™ in study participants with unresectable locally advanced pancreatic adenocarcinoma who received gemcitabine + nab-paclitaxel chemotherapy), with an almost identical design to the PanCO study.[3] The study recruited 9 participants between February and November 2018, across 4 centers in the US. The primary objective of the study was to evaluate the safety/tolerability of OncoSil™ when added to contemporary systemic chemotherapy regimens, and the feasibility of the device and EUS-directed implantation.

RAH/NZ Study

A real-world independent, retrospective, investigator-initiated study was conducted at two centers (the Royal Adelaide Hospital, Australia and Waikato Hospital, New Zealand; ['RAH/NZ' study]) on the outcomes in patients receiving OncoSil™ in clinical practice for the treatment of unresectable LAPC.[4,5] A total of 101 patients were included in a propensity-score analysis, of which 90 comprised a matched pair cohort [45 that received OncoSil™ plus chemotherapy versus 45 that received standard therapy (chemotherapy ± chemoradiotherapy)]. The primary outcome was overall survival (OS) with secondary corroborating /supportive outcomes of progression-free survival (PFS), downstaging of disease, and local disease control.

OSPREY Registry

The OSPREY Registry is a company-sponsored, post-market observational study being conducted in the EU and UK to provide real-world evidence on the outcomes in patients receiving OncoSil™ added to gemcitabine-based chemotherapy for the treatment of unresectable LAPC.[3] The registry commenced enrolling patients in April 2022 and is on-going. A total of 67 patients were treated through June 2025; 31 patients who received OncoSil™ within 6 months of commencing chemotherapy were evaluated for overall survival (OS) and target tumor (local) disease control: $LDCR_{16\ weeks}$ (12 weeks post-implantation).

10.1 Safety

10.1.1 Differentiating Toxicity Due to OncoSil™ and Chemotherapy

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 chemotherapy, differentiating toxicities due to the device and chemotherapy is relevant to the assessment of safety. In order to provide a positive benefit-risk profile, the toxicities (AEs) due the addition of OncoSil™ to the chemotherapy regimen should not result in a significant increase in toxicities above that expected for chemotherapy alone, relative to the clinical benefit of OncoSil™. Since the addition of OncoSil™ to the chemotherapy regimen cannot be blinded to the treating clinician (both PanCO and OncoPac-1 were single-arm, open-label designs), there is a potential for increased vigilance toward attributing toxicity to the investigational device. The toxicity profile of chemotherapy for the treatment of LAPC is well known to practicing Medical Oncologists and reported extensively in the literature. For the PanCO and OncoPaC-1 studies, Medical Oncologists attributed Treatment-Emergent Adverse Events (TEAEs) according to the following causalities: (1) OncoSil™ and/or the implantation procedure; (2) OncoSil™ and chemotherapy; (3) Chemotherapy only; (4) Neither OncoSil™, the implantation procedure, nor chemotherapy. Notwithstanding the Medical Oncologist's familiarity with the toxicity profile of Standard-of-Care chemotherapy, if there was a significant increase in the frequency or severity (Grade ≥3) of TEAEs associated to either OncoSil™ alone or OncoSil™ and chemotherapy compared to chemotherapy alone, this would raise concerns regarding the safety of OncoSil™.

10.1.2 Treatment-Emergent Adverse Events Reported for the PanCO and OncoPaC-1 Studies

Table 1 provides a summary of Treatment-Emergent Adverse Events (TEAEs) experienced by patients receiving OncoSil™ according to the causalities identified in **Section 10.2.1** above for the PanCO and OncoPaC-1 studies.

The safety of OncoSil™ can be assessed by examining the proportion and severity of TEAEs resulting from the integration of OncoSil™ into the standard chemotherapy regimen for LAPC. As shown in **Table 1**, the vast majority of TEAEs reported during the PanCO and OncoPaC-1 studies were attributed by investigators as being possibly or probably related to chemotherapy (754 of 1187 events; 63.5%) and these affected all study participants. Only 5.1% of the overall TEAEs reported (60 of 1187; 5.1%) were attributed as being possibly or probably related to OncoSil™ and/or the implantation procedure, and two-thirds of these (41 of 60; 68.3%) were also attributed as being possibly or probably related to chemotherapy. When the toxicity burden for patients was examined, 100% (n=51) experienced TEAEs related to chemotherapy, whereas 43.1% (n=22/51) experienced TEAEs related to OncoSil™ and/or the implantation procedure. When severity of toxicities was examined, 70.6% (n=36/51) of patients receiving chemotherapy experienced Grade ≥3 events, whereas 9.8% (5/51) experienced Grade ≥ 3 events related to OncoSil™ and/or the implantation procedure.

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

Category	PanCO + OncoPaC-1 [2,3] (PP: n=51) (OncoSil™ + Chemotherapy)	
	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 2 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. The overall frequency of TEAEs irrespective of causality and the frequency of TEAEs attributed to OncoSil™ + chemotherapy and chemotherapy are presented for comparison. As shown in **Table 2**, the majority of TEAEs experienced by patients were related to chemotherapy alone in comparison to chemotherapy + OncoSil™. This trend was consistent across all body systems and preferred terms.

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.

Eight and seven Grade ≥3 TEAEs were reported, respectively, in the PanCO and OncoPaC-1 studies with a possible or probable causality to OncoSil™ and/or the implantation procedure, which occurred in three (7.1%;) and two (22.2%) of the implanted PanCO and OncoPaC-1 study participants, respectively. Of note,

six of the eight Grade ≥3 TEAEs in the PanCO study were reported in the same participant. In comparison, 67 and 29 Grade ≥3 TEAEs, respectively, were attributed to chemotherapy, respectively, in the PanCO and OncoPaC-1 studies, in 28 (66.7%) and eight (88.9%) of the participants.

As anticipated, the TEAEs attributed as possibly or probably related to chemotherapy included large proportions of patients reporting fatigue (74.5%), gastrointestinal (GI) disorders (82.4%) including nausea (51.0%) and diarrhea (43.1%), blood & lymphatic system disorders (60.8%) including neutropenia (52.9%), thrombocytopenia (37.3%) and anemia (31.4%), decreased appetite (37.3%), alopecia (37.3%) and rash (29.4%). The most common Grade ≥3 TEAEs attributed to chemotherapy were neutropenia (41.2%), anemia (15.7%) and fatigue (9.8%).

Table 2: Treatment-Emergent AEs (TEAEs/TESAEs): Incidence Overall and Causality Attributed to OncoSil™/Implantation or Chemotherapy

Study	Pooled Analysis of TEAEs: PanCO/OncoPaC-1 Studies [2,3]					
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** (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 oedema [*]	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%)**

Study	Pooled Analysis of TEAEs: PanCO/OncoPaC-1 Studies [2,3]					
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** (n=51; GNP=43; FFX=8)	
TEAE/TESAE Category, n (%)	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Peripheral neuropathy *	17 (33.3%)	1 (2.0%)	-	-	17 (33.3%)	1 (2.0%)
Dysgeusia	7 (13.7%)	-	-	-	7 (13.7%)	-
Paraesthesia	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%)
Dyspnoea	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%)
Haemoglobin 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).

10.1.3 Adverse Events for OncoSil™ + Chemotherapy Compared to Chemotherapy Alone in Pivotal Phase III Randomized Controlled Trials

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 RCTs of FOLFIRINOX and gemcitabine + nab-paclitaxel that established the standard of care for pancreatic cancer (**Table 3**).

This comparison demonstrated that despite the addition of OncoSil™ to chemotherapy the proportion of AEs was comparable to or lower than those receiving chemotherapy alone in the Phase III trials.

Table 3: 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 [2,3] (OncoSil™ + Chemotherapy) (N = 51)	Pivotal Pancreatic Ca Phase III RCTs [8,9] (Chemotherapy Alone) (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.

10.1.4 In-Depth Analysis of Gastrointestinal and Pancreatic (Biliary- and Stent-Associated) AEs/TEAEs

Gastrointestinal TEAEs

Specific gastrointestinal (GI) TEAEs were anticipated following OncoSil™ implantation or were anticipated endoscopy procedure-related risks. However, gastrointestinal (GI) TEAEs reported in the PanCO and

OncoPaC-1 studies were also analyzed in order to identify any potential association with unanticipated GI TEAEs.

Anticipated GI TEAEs were attributed by investigators to OncoSil™ and/or the implantation procedure in the following proportion of implanted study participants:

- Abdominal pain (upper or unspecified): 5.9%, including 2.0% Grade ≥3
- Abdominal distension: 2.0%
- Diarrhea: 2.0%, including 2.0% Grade ≥3
- Nausea: 5.9%
- Vomiting: 0%

Anticipated endoscopy procedure-related GI TEAEs were attributed by investigators to OncoSil™ and/or the implantation procedure in the following proportion of implanted study participants:

- Dyspepsia: 3.9%
- Dysphagia: 2.0%
- Reflux gastritis: 2.0%
- Stomatitis (including mouth ulceration): 2.0%

The incidence of GI TEAEs attributed to OncoSil™ and/or the implantation procedure was lower than predicted, which was based on previous studies and the experience with radioembolization in the treatment of hepatic tumors. Some GI TEAEs such as abdominal pain and discomfort (as well as non-GI TEAEs such as fatigue and pyrexia) may be a consequence of the tumoricidal treatment effect from OncoSil™ and/or accompanying inflammation. Likewise, other GI TEAEs such as dyspepsia, dysphagia, stomatitis and reflux gastritis (plus the non-GI TEAEs of oropharyngeal pain and dysphonia) can be anticipated as known endoscopy procedure-related risks.

There were no other GI TEAEs in the PanCO and OncoPaC-1 studies where causality was attributed to OncoSil™ and/or the implantation procedure. However, all GI TEAEs were analyzed, irrespective of causality, in order to identify any association with unanticipated GI TEAEs.

- Duodenal obstruction: 2.0%
  - One study participant presented with a Grade 3 duodenal obstruction TESAE 2 days after commencing chemotherapy (and therefore prior to OncoSil™ implantation). This was determined by the investigator to be not treatment-related.
- Duodenitis: 2.0%
  - One study participant reported a Grade 3 duodenitis TESAE 6.8 months post-enrolment (6 months post-implantation) and 1.7 months after completing 6 cycles of gemcitabine + nab-paclitaxel chemotherapy. The TESAE was determined by the investigator to be not treatment-related.
- Epigastric discomfort: 2.0%
  - One study participant reported a Grade 2 epigastric discomfort TEAE 9.6 months post-enrolment (8.5 months post-OncoSil™ implantation). At this stage the study participant had developed liver metastases and was initially reported as a ‘late radiation-related AE’. The investigator subsequently considered that this TEAE was not related to OncoSil™, the implantation procedure or chemotherapy, although the participant previously had a Grade 3 upper GI hemorrhage TESAE that was determined to be possibly related to chemotherapy.

- Gastritis: 0 TEAEs
  - There were no gastritis TEAEs reported in either study.
- Obstruction gastric: 3.9%
  - One study participant was admitted to hospital with a Grade 3 obstruction gastric TEAE (gastric outlet obstruction) TESAE 3.1 months post-enrolment (2.2 months post-OncoSil™ implantation). This was determined by the investigator to be possibly related to chemotherapy which was temporarily halted at that stage. The same participant presented with a Grade 2 gastric obstruction 3.3 months later. This TEAE was determined by the investigator to be not treatment-related.
  - Another study participant presented with a Grade 3 obstruction gastric TEAE (gastric outlet obstruction) 2–3 months post-enrolment (precise date unknown; 1–2 months post-OncoSil™ implantation). As a consequence of pancreatic cancer, the participant had a duodenal stent inserted 1.5 months prior to commencing study chemotherapy. This duodenal stent had to be replaced 1.3 months post-enrolment, again due to pancreatic cancer. A further duodenal stent insertion was performed 3.2 months post-enrolment to resolve the gastric outlet obstruction. The investigator determined that the Grade 3 gastric obstruction was not treatment-related.
- Upper gastrointestinal hemorrhage: 2.0%
  - One study participant reported a Grade 3 upper GI hemorrhage TESAE 5.2 months post-enrolment (4.2 months post-OncoSil™ implantation) that was determined to be possibly related to chemotherapy.

There is no evidence 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. A detailed analysis of biliary and pancreatic TEAEs follows in the subsequent sub-section.

Pancreatic-, Biliary- and Stent-Associated AEs/TEAEs

Pancreatitis was reported in 4 PanCO study participants (5.9%). No pancreatitis AEs/TEAEs were reported in OncoPaC-1 study participants. All the pancreatitis AEs were prior to enrolment or recurred post-enrolment in 1 participant who did not receive OncoSil™ due to pancreatitis. The two (2) recurrent pancreatitis TEAEs in this participant were attributed to chemotherapy by the investigator.

Peri-pancreatic fluid collection was reported in 2 (3.9%) participants; neither were related to treatment, with 1 a Grade 1 AE 7.7 months post-OncoSil™ implantation and the other a Grade 3 TEAE occurring following surgical resection. Peri-pancreatic fluid collection is a known complication following a Whipple's procedure (pancreaticoduodenectomy).

Eleven study participants (21.6%) had biliary TEAEs. The most common biliary TEAE was blocked, obstructed or occluded biliary duct (15.7%), and biliary sepsis (5.9%), which are anticipated events in patients with pancreatic cancer. Biliary sepsis was associated with duct occlusion, liver abscess, or pancreatitis (in a participant that did not receive OncoSil™). Bile duct stones (choledocholithiasis) were reported in 2 study participants (3.9%); one of which was attributed to chemotherapy and the other occurred prior to OncoSil™.

One Grade 1 biliary stent-related hemorrhage was reported in a participant 2.9 months post-OncoSil™ implantation.

Between a quarter and a third of PanCO and OncoPaC-1 study participants had biliary or pancreatic duct stents at enrolment or prior to OncoSil™ implantation (16/51 [31.8%]).

Five study participants (5.9%) had a new stent or underwent stent revision less than 1 month prior to enrolment or prior to OncoSil™ implantation. Only 1 participant (2.0%) had a new stent inserted post-OncoSil™ implantation, 1 (2.0%) had a stent removed post-OncoSil™ implantation and 5 (8.5% ITT; 9.8% PP) participants had stents replaced during the longer follow-up period post-OncoSil™ implantation. The pattern of presentation with biliary or pancreatic duct stents, and the subsequent occlusion requiring revision or replacement was consistent with the natural history of patients with pancreatic cancer.

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.

There is no evidence to suggest any negative effects from OncoSil™ and/or the implantation procedure on biliary or pancreatic duct stents, duct occlusion, or any association with biliary or pancreatic adverse events.

Summary of Analysis

In-depth analysis of gastrointestinal AEs, as well as pancreatic, biliary and stent-associated AEs confirmed there was no evidence to suggest any negative effects from OncoSil™ and/or the implantation procedure on the pancreas, bile duct or GI tract, including existing or new biliary/pancreatic stents, or any association with biliary, duodenal, gastric or pancreatic AEs. There were no deaths related to OncoSil™, the implantation procedure or associated chemotherapy. There were no radiation-induced adverse events reported for any patient treated with OncoSil™.

Summary Safety Analysis of the PanCO and OncoPaC-1 Studies

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 number of AEs attributed to OncoSil™ and/or the implantation procedure was small (60 across the 2 studies, or 5.1% of total AEs), anticipated and were typically transient in nature, self-limiting and conservatively managed (medically). For comparison, the number of AEs attributed to chemotherapy was 754 (or 63.5% of total AEs). A disproportionate number of AEs (366; 30.8%) occurred in the short time-period (median 1.0 month) prior to OncoSil™ implantation, compared to the remaining AEs that were spread over a median follow-up of more than 2 years.

10.1.5 Additional Safety Data from DB2-201, DB2-202, and the Real-World 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 LAPC patients treated with chemotherapy in the RAH/NZ study from August 2017 to January 2023, no (0) acute complications and no (0) OncoSil™- or procedure-related Grade ≥3 AEs were reported.

In the OSPREY registry, there was no evidence of safety concerns or unexpected/serious toxicities associated with OncoSil™ in clinical practice. For 67 patients treated from April 2022 to June 2025, 10

(14.9%) experienced Grade 1–2 AEs attributed to OncoSil™ and/or the implant procedure (9 patients had Grade 1 abdominal pain; 1 had Grade 2 fatigue), with no serious adverse events (SAEs) reported.

10.1.6 Standard-of-Care Regimens for the Treatment of LAPC and dCCA

Given the anatomic, physiological, and functional similarities of LAPC and dCCA, clinical studies of OncoSil™ in treating LAPC have been utilized to support safety and probable benefit of OncoSil™ for use in in patients with unresectable locally advanced dCCA.[9] Chemotherapy regimens for LAPC and dCCA are similarly based on a backbone of gemcitabine in conjunction with nab-paclitaxel for LAPC and cisplatin for dCCA, respectively.

To provide some perspective on the safety profiles of gemcitabine + nab-paclitaxel compared to gemcitabine and cisplatin, the AEs for these two regimens were compared. **Table 4** presents the most common Grade ≥3 treatment-emergent AEs for the PanCO/OncoPaC-1 studies incorporating OncoSil™, the Von Hoff study which established gemcitabine + nab-paclitaxel as the standard-of-care (SOC) for pancreatic cancer, and the pivotal study by Valle et al which established gemcitabine + cisplatin as the SOC for biliary tract cancer (cholangiocarcinoma).[9,10]

The pivotal study by Valle et al 2010 examined the safety and efficacy of gemcitabine plus cisplatin (n=204) compared to gemcitabine alone (n=206) in patients presenting with locally advanced or metastatic biliary tract cancer (cholangiocarcinoma, gallbladder cancer, or ampullary cancer).[10] The median overall survival for the gemcitabine-cisplatin group was 11.7 months *vs.* 8.1 months for the gemcitabine group, respectively (hazard ratio: 0.64; 95% CI 0.52 to 0.80; p<0.001). An examination of the AEs for the Valle et al study indicates that the nature and frequency of AEs for the gemcitabine + cisplatin regimen is similar to that for the gemcitabine + nab-paclitaxel regimen in both the PanCO/OncoPaC-1 and Von Hoff studies (**Table 4**). This would be expected on the basis that the two regimens comprise a backbone of gemcitabine. In addition, both paclitaxel and cisplatin have radio-sensitizing effects. With the exception of neutropenia and anemia, the proportion of AEs for the PanCO and OncoPaC-1 studies are comparable to or lower than those reported for both the Von Hoff and Valle studies.

Based on the similarity in the nature and frequency of adverse events for the gemcitabine + nab-paclitaxel and gemcitabine + cisplatin regimens, the integration of OncoSil™ into the respective regimens is not expected to result in any unanticipated safety concerns. Given the extremely poor prognosis for dCCA, the potential benefit of OncoSil™ in combination with chemotherapy would outweigh any risks associated with the treatment.

Table 4: Grade ≥3 Treatment-Emergent Adverse Events of Interest, As Reported in the PanCO and OncoPaC-1 Studies, Von Hoff 2013, and Valle 2010 Studies

Study	PanCO +OncoPaC-1 Studies [2,3] (LAPC)	Von Hoff 2013 [9] (LAPC)	Valle 2010 [10] (Biliary Tract Cancer/ Cholangiocarcinoma)
Therapy	**OncoSil™ + gemcitabine + nab-paclitaxel [a]**	**gemcitabine + nab-paclitaxel**	**gemcitabine + cisplatin**
	(N = 43)	**(N = 421)**	**(N = 198)**
TEAE leading to death	0% (0)	4.3% (18/42)	nr
Grade ≥3 hematological TEAEs			
Neutropenia	46.5% (20/43) [b]	37.8% (153/405)	25.3% (50/198)
Febrile neutropenia	4.7% (2/43) [b]	nr	nr
Leukopenia	11.6% (5/43)	30.6% (124/405)	15.7% (31/198)
Thrombocytopenia	11.6% (5/43)	12.8% (52/405))	8.6% (17/198)
Anemia	23.3% (10/43)	13.1% (53/431)	7.6% (15/198)
Grade ≥3 non-hematological TEAEs occurring in >5% of patients			
Fatigue	9.3% (4/43)	16.6% (70/421)	18.7% (37/198)
Peripheral neuropathy	2.3% (1/43) [d]	16.6% (70/421)	nr
Diarrhea	4.7% (2/43) [d]	5.7% (24/421)	nr
Vomiting	6.9% (3/43)	nr	5.1% (10/198)
Elevated level of alanine aminotransferase	2.3% (1/43)	nr	9.6% (19/198)
Thromboembolism	0% (0) [c]	nr	3.5% (7/198) [d]
Nausea	6.9% (3/43)	nr	4.0% (8/198) [d]
Biliary sepsis	4.7% (2/43)	nr	4.0% (8/198 [d]

[a] In PanCO, chemotherapy could be either gemcitabine + nab-paclitaxel (n=34) or FOLFIRINOX (n=8) [PP population]; in OncoPaC-1, all patients n=9) received gemcitabine + nab-paclitaxel. This table presents the rates for patients receiving gemcitabine + nab-paclitaxel.
[b] In PanCO & OncoPaC-1, the rates for neutropenia (which includes TEAEs reported as neutropenia, neutropenic colitis, neutropenic sepsis and/or neutrophil count decreased) and febrile neutropenia are shown separately.
[c] In PanCO, 5 patients (11.9%) had pulmonary embolism.
[d] Adverse event reported in < 5% of patients.
Abbreviations: nr, not reported; TEAE, treatment-emergent adverse event.

10.2 Probable Benefit

The probable benefit of OncoSil™ was based on studies of patients with locally advanced pancreatic cancer. Therefore, data on the probable benefit of OncoSil™ in dCCA is not available. Given the anatomic, physiological and functional similarities of LAPC and dCCA, the data on LAPC are supportive of, and are clinically relevant to, an assessment of probable benefit of OncoSil™ in treating the dCCA population.[1]

The probable benefit of OncoSil™ is supported by the results of two prospective open-label, single-arm studies (PanCO and OncoPaC-1), a retrospective real-world study (RAH/NZ) and a prospective real-world registry (OSPREY). A summary of results for these studies and the registry is provided in **Table 5** and **Figure 1**.

Currently, there are no data on the probable benefit of OncoSil™ in patients with dCCA. The clinical evidence therefore includes LAPC studies using the same EUS-guided intratumoral implantation technique in anatomically adjacent pancreaticobiliary tumors. These data are relevant because they support implantation feasibility, OncoSil™- and procedure-related safety, and local tumor control after intratumoral delivery of OncoSil™, while recognizing the limitations of extrapolating from LAPC to dCCA. LAPC outcomes are presented as supportive evidence for local intratumoral treatment effect and feasibility in pancreaticobiliary anatomy.

The efficacy endpoints summarized in **Table 5** (overall survival [OS], progression-free survival [PFS], local disease control, local progression and tumor response) are clinically relevant in unresectable dCCA, where morbidity and mortality are primarily driven by local tumor progression and biliary obstruction. Improved local disease control and delayed progression may preserve biliary patency, reduce complications such as jaundice and cholangitis, and support continuation of systemic chemotherapy. Tumor response and disease stabilization may also contribute to symptom control. In addition, downstaging and conversion to resectability, observed in a subset of patients, are clinically meaningful given that surgery is the only potentially curative option. Collectively, these outcomes support a probable clinical benefit of OncoSil™ in the HDE population, where demonstration of effectiveness is not required.

PanCO Study

A median overall survival of 15.5 months (95% confidence intervals [CI]; 11.4–20.1), median overall PFS of 9.3 months (95% CI: 5.8–11.3) and median local PFS of 9.8 months (95% CI: 7.3–12.6) were reported. The objective response rate was 31.0% (95% CI: 17.6–47.1), with one in three patients (33.3%) being technically resectable and 23.8% (95% CI: 12.1–39.5) surgically resected. Of the 10 study participants who underwent surgical resection following OncoSil™, R0 resection margins were achieved in 8 (80%) of these cases; 6 of the resected participants were alive at study completion 26.4–35.3 months post-enrolment, with 5 having no disease recurrence.

OncoPaC-1 Study

Despite the small sample size, efficacy outcomes in the study were generally in line with the PanCO study. Median LPFS and PFS were 27.3 and 12.2 months, respectively, and median overall survival was 27.3 months.

Table 5: 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 [4,5]			OSPREY Registry [3]
	PanCO [2] OncoSil™ + Chemotherapy (N=42)	OncoPaC-1 [3] 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.

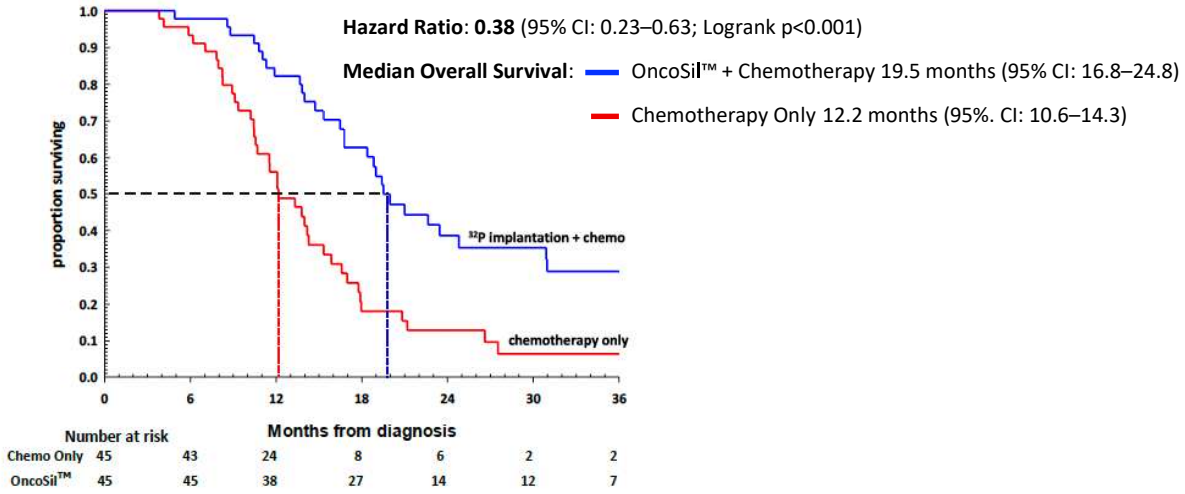


Figure 1: Kaplan-Meier Overall Survival Curves for the Propensity Matched Population

RAH/NZ Study: Propensity Score Matched Pair Analysis

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.[4,5] The overall survival for the OncoSil™ + chemotherapy group exceeded that of the chemotherapy group as measured by Kaplan-Meier analysis (median 19.5 *vs*. 12.2 months, respectively, p<0.001) [**Figure 1**]. 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).

OSPREY Registry

Median overall survival for 31 patients implanted with OncoSil™ within 6 months of commencing chemotherapy was 18.0 months (95% CI; 16.9–23.8). The cohort had a local disease control rate at 12 weeks post-implantation of 90.5% and a 21.7% objective response rate compared to baseline imaging immediately prior to implantation.

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).

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.

10.2.1 Comparison of OncoSil™ with Standard Therapy for Unresectable LAPC

As shown in **Table 6** the clinical benefit for OncoSil™ reported in the PanCO study demonstrates probable benefit as compared to Standard-of-Care (SOC) treatments for unresectable LAPC. The PanCO study OS (15.5 months [95% CI; 11.4–20.1]) exceeded that of NCCN guideline chemotherapy and ICT + CCRT regimens included in a meta-analysis (12.9 months [95% CI; 12.6–13.6]).[2,3] In addition, the trend for overall survival is also applicable to the OncoPaC-1 study (27.3 months), RAH/NZ study (19.5 months) and OSPREY registry (18.0 months).[3,4,5] For 9 selected US studies from another meta-analysis of unresectable LAPC patients receiving neoadjuvant therapy, the median OS was reported at 14.3 months which was exceeded by the median OS of both the OPSREY registry (18.0 months) and the RAH/NZ study (19.5 months).[5]

Table 6: Efficacy Outcomes in Patients Treated with OncoSil™ + Chemotherapy (PanCO Study), Compared with the Meta-Analysis of Phase II/III Study Arms of Chemotherapy and Chemoradiotherapy (CCRT) Regimens Included in the Current NCCN Guidelines for Locally Advanced Pancreatic Cancer

Parameter of Interest	PanCO Study OncoSil™ + chemotherapy (95% CI) [2] (N=42) [a]	Meta-Analysis of LAPC for NCCN Guideline chemotherapy and ICT + CCRT regimens (95% CI) [3] (N≤1,809)
Median Overall Survival (mOS)	15.5 months (11.4–20.1)	12.9 months (12.6–13.6)
Median Progression-Free Survival (mPFS) [be]	9.3 months (5.8–11.3)	7.1 months (6.8–7.8)
One-Year Survival (%)	64.3% (47.9–76.7)	53.6% (47.9–59.3)
Disease Control Rate (DCR) (%) [bcd]	100% (91.6–100)	74.7% (57.2–89.0)
Overall Response Rate (ORR) (%) [bcd]	31.0% (17.6–47.1)	14.2% (8.0–21.6)

Resection Rate (%)	23.8% (12.1–39.5)	8.7% (5.4–12.5)

Abbreviations and Key: LAPC, locally advanced pancreatic cancer; ICT, induction chemotherapy; ICT+CCRT, induction chemotherapy plus concurrent chemoradiotherapy; 95% CI, 95% confidence interval; [a] per protocol population; [b] by central image reader analysis of CT imaging using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; [c] percentages based on the number of all study recipients; [d] response prior to surgical resection; [e] uncensored for resection.

11. CERTIFICATION OF TREATMENT FACILITIES AND PERSONNEL

OncoSil™ is to be used in a licensed treatment facility. These facilities must hold an appropriate license for the isotope Phosphorous-32 (^{32}P), which mandates that these institutions will have an appointed Radiation Safety Officer (RSO) / Radiation Protection Officer (RPO) who will be the primary contact for all matters related to radiation safety.

The OncoSil™ suspension should be prepared within the Nuclear Medicine Department or within a licensed Radiopharmacy. Only appropriately licensed personnel, who have been trained in the preparation of the OncoSil™ suspension may prepare the product for implantation.

As the implantation and handling of OncoSil™ involves a multi-disciplinary team approach, the following personnel may be expected to undertake the OncoSil Medical Training Program:

- Nuclear Medicine Personnel (Physician, Physicists, Technologists, Radiopharmacist)
- Radiation Safety Officers (RSO) / Radiation Protection Officer (RPO)
- Radiation, Medical and Surgical Oncologists
- Interventional Radiologists
- Endoscopist
- Procedural staff (nurses, anesthetists)

OncoSil Medical can only authorize a shipment of OncoSil™ after:

1. The license for the treatment facility to receive and hold ^{32}P has been verified by OncoSil Medical.
2. A training visit has been conducted in which relevant individuals permitted to work as an Authorized Dispenser (AD), Authorized User (AU) and surgical/procedural personnel etc. have completed the training and experience set out by OncoSil Medical. Please see below.
3. The treatment facility has calibrated their ion chamber using the OncoSil™ Calibration System.

11.1 Authorized Dispenser and Authorized User

Authorized Dispenser (AD)

- **Definition of Authorized Dispenser (AD)** as defined by OncoSil Medical, is the person preparing the OncoSil™ suspension (i.e., Radiopharmacist, Nuclear Medicine Personnel) and must successfully complete additional training on OncoSil™ as described below;

AD Training: The AD attends the OncoSil Medical Training Program and performs at least one cold dose (i.e. Microparticles are not radioactive) dilution which is supervised by an OncoSil Medical representative (Authorized Trainer).

Authorized User (AU)

- **Definition of Authorized User (AU)** As defined by NRC Regulations Title 10, Code of Federal Regulations (10 CFR 35.2) and must have successfully completed additional training on OncoSil™ as outlined below;

AU Training: In order to become a fully accredited Authorized User, the AU attends the OncoSil Medical Training Program and must perform their first patient implantation under the supervision of an OncoSil Medical representative (Authorized Trainer).

Note: In some cases, the AD and the AU may be the same person. If so, they will be required to complete both OncoSil Medical Training Program in order to be accredited in both roles.

All personnel must be trained by an OncoSil Medical representative (Authorized Trainer). Supplemental training may be required if significant revisions are made to existing procedures by the company.

The AD and AU will each receive accreditation from OncoSil Medical to document that they are authorized to order and handle OncoSil™.

12. STORAGE AND TRANSPORTATION CONDITIONS

Upon receipt of the OncoSil™ System and once incoming inspection requirements are fulfilled, the device should be stored inside the Type A packaging and moved to Nuclear Medicine Department/ Radiopharmacy, or other approved location that is able to handle radioactive materials until the OncoSil™ suspension is to be prepared.

The Microparticles and Diluent should be stored at room temperature. **Do not freeze the Diluent.**

13. DEVICE PRESENTATION

Each OncoSil™ System will be labelled with the product code **OS01** and will contain the following components:

- 1 sealed can encasing 1 x vial of the Microparticles containing 250 ±10% MBq at 11:00 AM (GMT) or 6:00 AM (EST) on the reference date. The vial is supplied inside a Acrylic lined lead pot.
- 2 vials of approximately 9 mL of OncoSil™ Diluent.
- 1 empty sterilized P6 vial for dilution of suspension of OncoSil™ (identified with a green stripe on the top of the label).
- 1 empty lead pot for dilution of suspension of OncoSil™ (identified with a green stripe on the top of the label).

14. ACCESSORIES

A number of accessories routinely available in Nuclear Medicine Departments/Radiopharmacy are used to prepare the OncoSil™ suspension. These accessories are not supplied with the OncoSil™ System. Examples include:

- Long forceps/tweezers with rubber tips (preferably 7.87 inches, to minimize radiation finger doses)
- Plastic backed absorbent surface covers
- Sterile Luer lock syringes (3 mL or 5 mL and 10 mL)
- Sterile 16–21 gauge needles, 1–2 inches in length
- Sterile aeration / filtered venting needles
- Sterile Isopropyl Alcohol (IPA) Wipes
- Beta radiation syringe shields (3 mL or 5 mL and 10 mL)

- Lead transport box
- Protective clothing (gloves, coats, goggles etc.)
- Three-way Luer lock tap

15. PATIENT SELECTION AND PRE-TREATMENT TESTING

Patients with unresectable dCCA tumors may be considered for treatment with OncoSil™. Unresectable locally advanced dCCA patients will typically present with the following clinical, imaging and hematologic signs:

- Biliary stricture/occlusion in the pancreatic head
- Absence of pancreatic duct dilation
- Normal appearing pancreas
- Elevated LFTs/bilirubin – jaundice

Target Tumor

In general, the target tumor should be:

- Chosen based on radiological investigation
- Visible on ultrasound imaging
- Judged to be technically accessible

It is recommended that the size of target tumor is under 2.7 inches (longest diameter) and under 110cc volume. There is limited experience implanting tumors of >50cc. In the clinical studies of OncoSil™, the median volume was 24cc.

A number of assessments are recommended prior to treatment with OncoSil™. These are often part of standard patient workup and include:

- Medical assessment of relevant patient's risk characteristics and contraindications (to confirm it is reasonable to undertake the implantation procedure). Refer to **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.
- PRECAUTIONS in Section 8.
- Histological or cytological confirmation of diagnosis
- Laboratory evaluation to ensure adequate hematological, renal and hepatic function
- Biochemical tests of pancreatic function (e.g. amylase, lipase)
- Coagulation profile
- Radiological investigations may include:
    - CT scans of the pancreas, thorax, abdomen, pelvis
    - CT imaging to determine tumor volume

16. CALCULATING ACTIVITY AND IMPLANTATION STRATEGY

Prior to patient implantation, OncoSil™ should be prepared within the Nuclear Medicine Department of the implanting treatment facility, or within a licensed Radiopharmacy. The Microparticles and Diluent are combined in accordance with the pre-defined **DETAILED SUSPENSION PREPARATION PROTOCOL** outlined in Section 17 below.

The implantable components of OncoSil™ are supplied sterile and are intended for single-patient, single-use. It is administered by direct implantation into the tumor (avoiding vessels), using the prepared suspension of OncoSil™ with a final radioactive concentration of 6.6 MBq/mL. The dose volume has an Implanted Volume/Tumor Volume (IV/TV) of 8%, to deliver 100 Gy to the tumor mass. In order to achieve this, the following steps need to be performed:

Estimation of Tumor Volume (TV)

Baseline tumor volume estimation for patients is the responsibility of the patient's treatment team.

Step 1 – First Dilution

The first dilution is to achieve a radioactivity in the range of 35.3 MBq/mL ± 0.59%

1. The initial dilution of the OncoSil™ Microparticles must be calculated using **Table 7 : Volume Required for the First Dilution of OncoSil™ Suspension** by adjusting the amount of Diluent added in accordance with the day the implantation will occur with respect to the reference date.
2. After completing the first dilution step as indicated above, the radioactivity of the first dilution should be in the range of 35.3 MBq/mL ± 0.59%.

Note: The reference date and time for OncoSil™ doses is Greenwich Mean Time at 11:00 AM or Eastern Standard Time at 6:00 AM. An adjustment should be made to measuring ionization chamber (or radioisotope dose calibrator) for different time zones around the world.

Table 7 : Volume Required for the First Dilution of OncoSil™ Suspension

Day of Implantation (Relative to Reference Date)	Aliquot of Diluent to Add (mL)	Vial Total Radioactivity (MBq)
-2	7.7	276
-1	7.3	262
0	7.0	250
+1	6.7	238
+2	6.4	227
+3	6.0	216
+4	5.8	206
+5	5.5	196
+6	5.2	187
+7	5.0	178

Step 2 – Second Dilution

The second dilution is to obtain the standardized concentration of 6.6 MBq/mL for administration.

1. Add 7.5 mL of Diluent to the empty P6 vial (identified with a green stripe on the top of the label).
2. Under aseptic conditions, draw up 1.7 mL of the first dilution prepared in step 1 above. Add the 1.7 mL to the P6 vial to give a final volume of 9.2 mL.
3. This now gives an OncoSil™ suspension of 6.6 MBq/mL on the day of implantation. This is the concentration required for administration.

OncoSil™ must be used within 24 hours of preparation, with exception if the preparation was performed +7 days from reference date. If the suspension is made on day +7 it must be used the same day.

Note: Once the day of implantation is chosen and the dilutions above have been performed the implantation date cannot be changed otherwise the concentration of 6.6 MBq/mL required for implantation will not be correct.

Step 3 – Determination of the Volume to be Implanted

Use the 2 equations shown below to calculate actual OncoSil™ volume to be dispensed and then implanted.

1. $OncoSil™\ Volume\ to\ be\ Implanted_{ml} = \text{Tumor Volume}_{\text{ml}} \times \frac{8}{100}$
2. $Activity\ \ to\ be\ Implanted_{MBq} = \text{OncoSil™ Volume to be Implanted}_{\text{ml}} \times 6.6$

Step 4 -Pre-Injection Confirmation

In order to confirm the radioactivity to be implanted into the patient:

1. Measure the total vial radioactivity of the P6 vial via the ionization chamber.
2. Draw up the required volume of OncoSil™ for implantation into the syringe.
3. Post syringe draw-up, measure the residual OncoSil™ suspension that remains in the P6 vial in the ionization chamber to confirm the amount drawn up/prepared for injection is correct.

Step 5 - Post-Injection Confirmation

To determine the total radioactivity delivered to the patient (total activity implanted in the tumor) is determined by subtraction of the post-implantation volume (mL) reading in the syringe from the pre-implantation volume (mL) within the syringe (i.e. an ionization chamber measurement is not required for syringe contents).

17. DETAILED SUSPENSION PREPARATION PROTOCOL

This section provides a detailed instruction for the preparation of OncoSil™ as calculated in Section16, above.

Note:

- The suspension preparation must be performed by the Authorized Dispenser trained by an OncoSil Medical representative.
- Suspension preparation is the responsibility of the treatment facility.
- Before beginning the procedure, the labelling of all components of the OncoSil™ System should be checked to ensure that the correct materials are available for use. Visually inspect the vials for cracks, breakages, and incomplete seal **prior** to use. If there is sign of damage, return the damaged component(s) to the radiation shields and contact OncoSil Medical.
- To minimize the risk of microbiological contamination, OncoSil™ should be prepared in a clean environment using standard techniques. For example, operators should wear fresh gloves and treat the gloves with a commercial bactericidal hand wash.
- The suspension procedure is to be performed behind acrylic, suitable for shielding from beta particles, under a fume hood.
- This procedure should **not** be performed under a laminar flow hood, which directs airflow towards the operator thereby risking exposure to radioactive material.
- All syringes must be used within an appropriate beta-radiation (acrylic or poly (methyl methacrylate) [PMMA)) syringe shield.
- All vials within the OncoSil™ System must only be used for a single preparation. All contaminated waste must be placed in a designated radioactive waste container.

- Upon withdrawing needles from vials, be aware of any drips of radioactive suspension from the needle tip that could drop onto the top of the vial or the bench.

Figure 2: The OncoSil™ System

Step-by-Step Procedure:

Contents: 1 sealed can encasing 1 x vial containing Microparticles @ 250 ±10% MBq supplied inside an acrylic lined lead pot, 2 vials of approximately 9 mL of OncoSil™ Diluent, 1 empty sterilized P6 vial for dilution of suspension of OncoSil™ (identified with a green stripe on the top of the label), 1 empty lead pot for dilution of suspension of OncoSil™ (identified with a green stripe on the top of the label).

1. Remove the components from the Styrofoam insert in the Type A package.
2. Hold the sealed can securely.
3. Pull ring and remove lid from the can.
4. Remove the packing material and the acrylic lined lead pot containing the Microparticles vial from the tin.
5. Place the can, lid and packing material in appropriate waste after checking for radioactive contamination.

Note: The initial preparation and the dilution to the standardized concentration of 6.6MBq/mL for administration should be done consecutively.

Note: A filtered/aeration venting needle should be used to assist with all steps of the dose preparation procedure.

Step 1 – First Dilution

6. **Microparticles Vial:** Take the acrylic lined lead pot that encloses the vial of Microparticles.
7. Remove the tape that's securing the top and bottom segments of the acrylic lead pot and CAREFULLY AND SLOWLY remove ONLY the lead lid from the pot.
   Note: that the lid is the larger lead segment.
8. The vial containing the Microparticles is itself contained within a further acrylic lined shield.
9. Using long forceps/tweezers remove acrylic lid only.
10. Using long tweezers, wipe the rubber stopper of the Microparticles vial with a sterile IPA wipe.
11. Using long forceps/tweezers replace acrylic lid.
12. **Diluent Vial:** Invert Diluent vial until the suspension is homogeneous.
13. Remove the plastic cap to expose the rubber stopper and wipe with a sterile IPA wipe.

14. Using a sterile 10 mL syringe with needle, draw up the required volume of Diluent (as per **Table 7 : Volume Required for the First Dilution of OncoSil™ Suspension**) and dispense through the small hole in the top of the acrylic lid into the Microparticles vial via its rubber stopper.
15. With the needle tip above the suspension, withdraw the air from the vial containing the Microparticles suspension, and expel any remaining diluent remaining in the needle. This step can be repeated if not all the Diluent is cleared from the syringe and needle.
16. With the needle tip above the suspension, pull back the syringe plunger to minimize the risk of drips from the needle tip, before CAREFULLY removing the needle from the vial.
17. Dispose syringes and needles in appropriate/radioactive waste.
18. Replace the lead lid of the pot.
19. **To assist mixing:** Firmly hold the top and bottom segments of the acrylic lined lead pot in a closed position and invert the suspension to obtain a homogeneous mixture. Do this 20-30 times.
20. Remove the lead lid of the pot and using long forceps/tweezers remove the acrylic lid.
21. Using long forceps/tweezers remove the Microparticles vial from the acrylic lined shield to check if suspension is homogeneous.
22. If the suspension is not homogeneous, replace Microparticles vial into acrylic lined shield, replace both the acrylic lid and lead lid of pot and repeat the inversion step until the suspension is homogeneous. Again, remove the lead lid from the pot and using long forceps/tweezers remove the acrylic lid and Microparticles vial to re-check if suspension is homogeneous.
23. Once homogeneous, using long forceps/tweezers, place the Microparticles vial into an OncoSil™ calibrated ionization chamber to verify the total vial radioactivity of the Microparticles from the first dilution. Refer to **Table 7 : Volume Required for the First Dilution of OncoSil™ Suspension** to verify the diluted vial total radioactivity (MBq) relative to the reference date.
24. Return the Microparticles vial back into the acrylic lined lead shield and replace the acrylic lid using long forceps/tweezers. Replace the lead lid of the pot.
25. Immediately prepare the second stage of the dilution process (see below).

Step 2 – Second Dilution

26. Take the empty acrylic lined lead pot.
27. Remove the tape that's securing the top and bottom segments of the lead lined pot and CAREFULLY AND SLOWLY remove ONLY the lead lid from the pot.
    Note: that the lid is the larger lead segment.
28. Remove acrylic lid.
29. Take the empty P6 vial (identified with a green stripe on the top of the label) and place into the acrylic shield within the empty lead pot.
30. Remove the plastic cap of the empty P6 vial to expose the rubber stopper and wipe with a sterile IPA wipe.
31. Replace the acrylic lid.
32. **SECOND Diluent Vial:** Invert second Diluent vial until suspension is homogeneous.
33. Remove the plastic cap of the empty vial to expose the rubber stopper and wipe with a sterile IPA wipe.
34. Using a sterile 10 mL syringe with needle, draw up 7.5 mL of Diluent and dispense into the empty P6 vial (identified with a green stripe on the top of the label) via the acrylic lid and rubber stopper.
35. With the needle tip above the suspension, withdraw the air from the vial, and expel any Diluent remaining in the needle.
    Note: this step can be repeated if not all the Diluent is cleared from the syringe and needle.

36. With the needle tip above the suspension, pull back the syringe plunger to minimize the risk of drips from the needle tip, before CAREFULLY removing the needle from the vial.
37. Dispose the syringes and needles in appropriate/radioactive waste.
38. **First Dilution:** Ensure suspension is homogeneous. If not, with both the acrylic lid and lead lid in place invert suspension 10–20 times or until homogeneous.
39. CAREFULLY and SLOWLY remove lead lid leaving the acrylic top in place.
40. Using a 3 or 5 mL beta-shielded syringe with a 5 cm long needle, remove 1.7 mL of the Microparticles suspension and transfer into the P6 vial which already contains 7.5 mL of Diluent, through the small hole in the top of the acrylic lid via the rubber stopper.
41. With the needle tip above the OncoSil™ suspension, withdraw the air from the vial, and expel any suspension remaining in the needle.
    Note: this step can be repeated if not all the OncoSil™ suspension is cleared from the syringe and needle.
42. With the needle tip above the suspension, pull back the syringe plunger to minimize the risk of drips from the needle tip, before CAREFULLY removing the needle from the vial.
43. Dispose the syringes and needles as radioactive waste.
44. Replace the lead lid of the pot.
45. **To assist mixing:** Firmly hold the top and bottom segments of the acrylic lined lead pot in a closed position and invert the suspension to obtain an homogeneous mixture. Do this 20–30 times.
46. Remove the lead lid of the pot and using long forceps/tweezers carefully remove the acrylic lid.
47. Using long forceps/tweezers remove the P6 vial containing OncoSil™ from the acrylic shield to check if suspension is homogeneous.
48. If the suspension is not homogeneous, replace the P6 vial containing OncoSil™ into the acrylic lined shield, replace both the acrylic lid and lead lid of pot and repeat the inversion step until the suspension is homogeneous. Again, remove the lead lid from the pot and using long forceps/tweezers remove the acrylic lid and the P6 vial containing the OncoSil™ to re-check if the suspension is homogeneous.
49. Once homogeneous, using long forceps/tweezers, place the P6 vial containing OncoSil™ into an OncoSil™ calibrated ionization chamber, to verify the total vial radioactivity of the Microparticles from the final dilution is 60 MBq per vial. Therefore, the final standardized concentration for administration is designed to be 6.6 MBq/mL on the day of implantation.
50. If the OncoSil™ suspension will not be immediately drawn up into the syringe used for implantation, return the OncoSil™ suspension vial back into the acrylic lined shield and replace the acrylic lid (using long forceps) and lead lid. Move the OncoSil™ suspension and store it in a suitable shielded location, until the suspension is ready to be administered.

Following preparation, the OncoSil™ suspension should be stored within the glass vial, inside the acrylic lined lead pot, at room temperature.

OncoSil™ must be used within 24 hours of preparation, with exception if the preparation was performed +7 days from reference date. If the suspension is made on day +7, it must be used the same day.

Dispose of all vials, acrylic lined lead pots, and packaging materials into appropriate radioactive waste and according to the treatment facility's radiation safety policy.

PREPARING THE BETA-SHIELDED SYRINGE AND DISPENSING OF THE ONCOSIL™ SUSPENSION

1. To ensure OncoSil™ is homogeneous, firmly hold the top and bottom segments of the acrylic lined lead pot in a closed position and invert the suspension to obtain an even mixture. Do this 10–20 times, or until homogeneous.

2. Label the empty beta-shielded syringe / transport box with a minimum of the following:
    a. Patient identifiers (initials)
    b. Name of the Radioactive Material (OncoSil™ Phosphorous-32 Microparticles)
    c. Syringe Volume (mL)
    d. Syringe calculated radioactivity (MBq)
    e. OncoSil™ expiry date and time
3. Place the empty syringe in an appropriate beta-shielded syringe and lock in place.
4. Attach a 7 cm long needle to the syringe within the beta-shielded syringe.
5. SLOWLY and CAREFULLY remove the lead lid (leaving the acrylic lid in place) from the acrylic lined lead pot containing the final OncoSil™ suspension.
6. If not already in place, insert a filtered aeration/venting needle through the hole in the top of the acrylic lid, into the rubber stopper of the P6 vial containing the final OncoSil™ suspension.
7. Using a 7 cm long needle, penetrate the P6 vial containing the final OncoSil™ suspension through the small hole in the acrylic lid and rubber stopper and draw up the required volume estimated from the tumor volume (from **Step 3 Determination of the Volume to be Implanted,** in **Section 16** into the beta-shielded syringe.
8. Once the OncoSil™ suspension is within the syringe, detach the needle and attach a three-way Luer tap to seal the end of the syringe.
9. Place the beta-shielded syringe in a lead transport box and transport to the procedure area.
10. Once the transport box reaches the procedure area, the beta-shielded syringe containing the OncoSil™ suspension should remain in the lead transport box until required for implantation.

Note: To ensure that the OncoSil™ suspension is homogeneous prior to implantation in the patient, hold the syringe at the body of the shield, being careful not to depress the syringe plunger, mix the OncoSil™ suspension by inverting the beta-shielded syringe three times, or until homogeneous.

18. IMPLANTATION PROCEDURE FOR ONCOSIL™ USING ENDOSCOPIC ULTRASOUND (EUS) GUIDANCE

The OncoSil™ implantation procedure must be performed in a suitable treatment facility environment and by a suitably qualified Endoscopist and the Authorized User (i.e., an OncoSil Medical trained Nuclear Medicine Physician/ Radiation Oncologist/ Interventional Radiologist).

A number of additional commercially available products are needed to implant OncoSil™ under endoscopic ultrasound (EUS) guidance. They do not form part of the OncoSil™ System and are not supplied by OncoSil Medical. They include:

- Echoendoscope
- A 22-gauge EUS guided FNA needle loaded through the biopsy channel of the echoendoscope or other equivalent device
- [Optional] A catheter extension set
- Syringes filled with saline
- Clinical waste-disposal bag lined with enough gauze to soak 50 mL of fluid
- Clinical waste-disposal bags for disposable accessories and protective clothing of procedure room staff
- Protective clothing (gloves, coats, goggles etc.)

If required, an extension set may be used, as shown below:

- Remove the beta-shielded syringe containing the OncoSil™ suspension from the lead transport box.
- Without depressing the syringe plunger, hold the beta-shielded syringe by its mid portion and mix the OncoSil™ suspension by inverting the beta-shielded syringe three times, or until homogeneous.
- [If using an optional catheter extension set] Remove the protecting Luer cap and attach a catheter extension set to the beta-shielded syringe with the three-way Luer lock tap to the distal end of the catheter extension set.
- Set the three-way Luer lock tap to the 'OPEN ' position.
- HOLDING THE BETA-SHIELDED SYRINGE BY ITS SIDES, KEEPING FINGERS AWAY FROM THE ENDS, position the syringe vertically, void ALL air remaining in the syringe by gently allowing the beta-shielded syringe plunger to press against a horizontal surface until the OncoSil™ suspension appears in the extension set tubing.
- Set the three-way Luer lock tap to the 'CLOSED' position.

Note: Whilst performing the above steps ensure that at all times the beta-shielded syringe is held by its mid portion. Throughout the procedure the operator should restrict exposure to axial radiation from the ends of the beta-shielded syringe.

Implantation Procedure:

1. The endoscope should be used in accordance with the detail guidance provided in the manufacturer's instruction manual (provided with the Endoscope).
2. Patient should be prepared in line with routine clinical practice.
   Note: Antibiotic prophylaxis to cover the OncoSil™ implantation procedure is advised. The selection and duration of antimicrobial regimen is based on local guidelines and practice.
3. The target dCCA tumor is identified on the ultrasound screen.
4. A 22-gauge EUS guided FNA needle is loaded through the biopsy channel of the echoendoscope and slowly advanced through the gastric wall or duodenal wall into the target dCCA tumor (avoiding damage to surrounding organs).
5. Once the FNA needle is in a satisfactory position within the tumor and avoiding vessels, the stylet is removed and a Luer tap is attached to the FNA needle.
6. To ensure the OncoSil™ suspension is homogeneous, hold the beta-shielded syringe by its mid portion and being careful not to depress the syringe plunger, mix the OncoSil™ suspension by inverting the beta-shielded syringe three times, or until homogeneous.
7. Remove the protecting Luer cap from the beta-shielded syringe containing the OncoSil™ suspension and attach the syringe to the FNA needle via the three-way Luer lock tap before setting the Luer tap to the 'open' position. Ensure that the syringe is securely attached to the three-way Luer lock tap.
8. The required amount of OncoSil™ suspension is then implanted manually by slowly depressing the plunger of the beta-shielded syringe.
   Note: If the resistance met prevents further OncoSil™ suspension from being expelled from the syringe, the needle should be slowly withdrawn within the tumor to a point where the syringe plunger can continue to be depressed (*see note below on backpressure).

9. Once the syringe is empty and the contents have been implanted into the tumor the three-way Luer lock tap is set to the 'closed' position.
10. The beta-shielded syringe containing the OncoSil™ suspension is removed from the three-way Luer lock tap and is re-capped and placed back into the lead transport box.
11. A 5 mL syringe containing saline should now be attached to the FNA needle via the three -way Luer lock tap and the tap re-set to the open position.
12. The remaining contents in the lumen of the FNA needle are then flushed with 1.5 mL of saline in order to flush any remaining OncoSil™ suspension from the needle lumen into the tumor.
13. Prior to removal of the scope from the patient, pull the endoscope back into the stomach, extend the needle sheath beyond the scope tip by about 3cm and flush with the remains of the saline syringe.
14. The tap is then set to 'closed'.
15. Re-sheath the needle, but do not remove the needle assembly from the scope.
16. Remove the scope with the FNA needle assembly in place and the needle sheath still extended beyond the scope tip.
17. Hold the scope tip with the extended needle sheath angled downwards over a clinical waste bag within which there is enough gauze to catch and hold any remaining fluid. Rinse the tip of the scope and sheath with the contents of a 50 mL syringe of water.
18. Once this is complete, remove the needle assembly from the scope and dispose of it in an appropriate radiation waste container.
19. Place the scope in an appropriate receptacle for transport for decontamination and cleaning.
20. The echoendoscope should be checked for radioactive decontamination prior to and after cleaning.
21. Wash and sterilize the echoendoscope using the standard method for cleaning the equipment at site.

Note: Regarding backpressure: If the resistance is too great on the subsequent implant attempt and it is not possible to empty the syringe contents into the tumor, the implantation procedure should be aborted. The syringe containing the OncoSil™ suspension should be removed as described above and the cap replaced before the syringe is placed back into the lead transport box for return to the Nuclear Medicine Department/Radiopharmacy to measure the volume to calculate the radioactivity remaining in the syringe. In these circumstances where the entire contents of the syringe was not implanted, this needs to be reported to OncoSil Medical (complaints@oncosil.com).

19. DISASSEMBLY OF THE SYRINGE AND SHIELD

THIS IS VERY IMPORTANT FOR RECONCILLIATION OF THE PATIENT DOSE BY THE NUCLEAR MEDICINE PERSONNEL

1. After completion of the implantation, the syringe containing any residual OncoSil™ suspension should be re-capped and then placed into the lead transport box.
2. Transfer to Nuclear Medicine Department/Radiopharmacy for measurement, and then decay.
3. The total radioactivity delivered to the patient (total activity implanted in the tumor) is determined by subtraction of the post-implantation volume (mL) reading in the syringe from the pre-implantation volume (mL) within the syringe (i.e. an ionization chamber measurement is not required for post-implantation syringe contents).

20. DISPOSAL OF EXCESS ONCOSIL™ SUSPENSION AND ACCESSORIES

Following dilution and implantation, any disposable needles/tubing, syringes with any remaining OncoSil™ suspension, gauzes, gloves, aprons and other protective clothing, must be disposed of as radioactive waste and in accordance with treatment facility policies.

21. STERILISATION OF THE ENDOSCOPE

Following the implantation procedure, the endoscope must be cleaned, washed and sterilized in accordance with local procedures.

The echoendoscope should be checked for radioactive contamination prior to and after cleaning.

22. POST-PROCEDURE RECOVERY

- The patient should be carefully monitored, through observation and recording of vital signs, as clinically indicated.
- The patient should be discharged from the department when they have recovered from the procedure.
- Depending on the patient's condition and the physician's assessment, they may be required to stay overnight at the treatment facility.
- SPECT-CT Bremsstrahlung imaging is advised following the implantation period prior to patient discharge to confirm satisfactory localization of radioactivity.

23. RADIATION SAFETY GUIDELINES FOR ONCOSIL™

All persons handling, dispensing and implanting OncoSil™ must be familiar with and abide by all Local, State and Federal regulatory requirements governing therapeutic radioactive materials. Standard approved radiation protection techniques should be used to protect staff when handling both OncoSil™ and the patient. For more specific guidance on radiation safety as it relates to the OncoSil™ System, refer to the OncoSil™ System Radiation Safety Guidelines.

23.1 General Precautions

- Adequate shielding from beta radiation must be effected during storage, handling and use of OncoSil™.
- Standard procedures and practices used to minimize occupational radiation doses must be effected during storage, handling and use of OncoSil™.
- Unshielded vials and syringes must be handled with forceps that set the fingers away from the unshielded radioactive source by a minimum of 20 cm.
- Care must be taken to ensure minimum radiation exposure to the patient extraneous to the therapeutic objective.
- Care must be taken to ensure minimum radiation exposure to all staff and other personnel who come into contact with the patient.
- Radiation safety practices must be implemented in accordance with Local, State and Federal, regulatory requirements. Any loss of containment (spills and/or leakages) of OncoSil™ must be isolated, contained and cleaned up immediately. Area contamination monitoring practices should then be followed to ensure the isolation, containment and cleaning has been effective.

- Standard clinical practice should be implemented with respect to the implantation delivery method used for OncoSil™.
- OncoSil™ must be prepared behind a screen suitable for shielding from beta particles e.g. Acrylic or Lucite.
- OncoSil™ must be stored inside adequate shielding at all times pre-and post-implantation.
- All contaminated waste must be placed in a designated radioactive waste container and disposed of in accordance with treatment facilities policies.

23.2 Patient and Visitors Precautions

- For vulnerable groups such as pregnant women, infants and children, the patient should avoid unnecessary contact for 2 weeks.

23.3 Staff Precautions

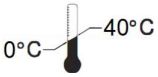
- Individual monitoring of personnel in accredited treatment facilities is a general requirement. There are no special requirements for personnel handling OncoSil™ in relation to radiation dose monitoring. General film badges or some form of personal dosimeter are acceptable.
- Nursing care and ward cleaning requirements will be at the discretion of the treatment facility's radiation safety procedures.

24. REFERENCES

1. Schmuck R, de Carvalho-Fischer C, Neumann C et al. Distal bile duct carcinomas and pancreatic ductal adenocarcinomas: Postulating a common tumor entity. Cancer Medicine 2016; 5: 88–99.
2. Ross P, Wasan H, Croagh D et.al. Results of a single-arm pilot study of ^{32}P microparticles in unresectable locally advanced pancreatic adenocarcinoma with gemcitabine/nab-paclitaxel or FOLFIRINOX chemotherapy. ESMO Open 2022 Feb; 7(1): 100356. doi: 10.1016/ j.esmoop.2021.1003511
3. OncoSil Medical Ltd., Data on file.
4. Lim A, Nitchingham D, Bednarz J et al. Combined phosphorus-32 implantation and chemotherapy versus chemotherapy alone for locally advanced pancreatic cancer: A propensity score–weighted landmark analysis. Gastrointestinal Endoscopy 2026; 103: 126–35.
5. Gebski V. Statistical Report: Benefits of OncoSil™ implantation within 6 months of commencing either gemcitabine ± nab-paclitaxel or FOLFIRINOX ± radiation therapy in patients with unresectable locally advanced pancreatic cancer (LAPC). September 2025.
6. American Joint Committee on Cancer (AJCC) TNM staging system, September 6, 2013. American Cancer Society. Available at http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-staging. Accessed: January 4, 2017.
7. National Comprehensive Cancer Network. Pancreatic cancer (version 1.2024). Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf Accessed August 4, 2024.
8. Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817–25. doi: 10.1056/NEJMoa1011923
9. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013; 369(18): 1691–703. doi: 10.1056/NEJMoa1304369
10. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010; 362: 1273–81. doi: 10.1056/nejmoa0908721

25. APPLICABLE SYMBOLS

	Do Not Re-Use
	Caution
	Radioactive Hazard
	Do not use if package is damaged
	Manufacturer combined with Date of Manufacture
	Catalogue number
	Serial Number
	Medical Device

	Use By Date
	Sterile Using Steam or Dry Heat
	This way up
	Temperature Limitation (upper and lower)
	Consult Instructions For Use (QR Code Link)
	MR Safe

OncoSil™ is a Registered Trademark of OncoSil Medical Ltd

OncoSil Medical Ltd.
Level 5, 7 Eden Park Drive
Macquarie Park NSW 2113
Australia
Tel: +61 2 8935 9629
www.oncosil.com

Level 5, 7 Eden Park Drive
Macquarie Park
NSW 2113
Australia

P +61 2 8935 9629

oncosil.com