REG-0002

Summary of Safety and Clinical Performance (SSCP) - OncoSil™ System

Version: 5

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1 Scope

The SSCP is intended to provide public access to an updated summary of clinical data and other information about the safety and clinical performance of the medical device.

2 Applicable Standards

External Document Reference		Document Title	Document Revision
[1].	***BS EN ISO 13485***	Medical devices — Quality management systems	2016+A11:2021
[2].	***BS EN ISO 14971***	Medical devices — Application of risk management to medical devices	2019+A11:2021
[3].	***BS EN ISO 14155***	Clinical investigation of medical devices for human subjects. Good clinical practice	2020
[4].	***Council Directive 2013/59/EURATOM***	Council Directive laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom	2013
[5].	***Council Directive 80/836/Euratom***	Council Directive 80/836/Euratom of 15 July 1980 amending the Directives laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation	1980
[6].	***Council Directive 84/467/Euratom***	Council Directive 84/467/Euratom of 3 September 1984 amending Directive 80/836/Euratom as regards the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation	1984
[7].	***Council Directive 84/466/Euratom***	Council Directive 84/466/Euratom of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment	1984
[8].	***Council Directive 90/385/EEC***	Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (AIMDD)	1990
[9].	***REGULATION (EU) 2017/745***	Regulation (EU) 2017/745 Of The European Parliament And Of The Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (MDR)	2017
[10].	***2002 No 618***	(UK) The Medical Devices Regulations 2002	2002
[11].	***MDCG 2019-9***	Summary of safety and clinical performance A guide for manufacturers and notified bodies	2019

3 The identification of the device and the manufacturer

Device Trade Name	**OS01-10 - *OncoSil™ System (EMEA)***
Manufacturer's name and address	**OncoSil Medical Ltd.** Level 5, 7 Eden Park Drive Macquarie Park NSW 2113 Australia
Manufacturer's SRN	AU-MF-000013395
Basic UDI-DI	9309000334OS01VC
Medical device nomenclature description / text	EMDN: J0501 Name: BRACHYTHERAPY SOURCES
Class of device	III
Year when the first certificate (CE) was issued covering the device	2020
Authorised representative name and the SRN	EU: **ICON LR Limited** South County Business Park, Leopardstown, Dublin 18, D18 X5R3 Ireland IE-AR-000006507 UK: **ICON (LR) Limited** 500 South Oak Way, Green Park Reading, RG2 6AD, United Kingdom
NB's name and the NB's single identification number	EU: **BSI Group The Netherlands B.V. - 2797** UK: **BSI Group UK - 0086**

Appendix A This section is intended for clinicians and healthcare workers

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https://www.oncosil.com/healthcare-professionals/#resources

A.1 The intended purpose of the device and any indications, contraindications and target populations

A.1.1 Intended Purpose

The OncoSil™ System is intended for the treatment of patients with locally advanced unresectable pancreatic cancer, in addition to gemcitabine-based chemotherapy, by inducing prolonged local tumour control and tumour size reduction via implantation of radioactive Phosphorous-32 microparticles into pancreatic tumours under endoscopic ultrasound guidance.

A.1.2 Indications for Use

OncoSil™ is indicated for the treatment of patients with locally advanced unresectable pancreatic cancer, in addition to standard of care chemotherapy.

A.1.3 Clinical Benefit

The goal of OncoSil™ treatment is to induce prolonged local tumour control and tumour size reduction by implantation of radioactive ^{32}P microparticles into pancreatic tumours under endoscopic ultrasound (EUS) guidance, delivering high doses of beta radiation to the target tumour.

A.1.4 Contra-indications

The device is contraindicated in patients who have a known history of hypersensitivity to silicon or phosphorous.

The device is contraindicated where endoscopic ultrasound (EUS) directed implantation is considered hazardous.

A.1.5 Intended Users

The Device is intended to be used only by Radiopharmacists, Nuclear Medicine Personnel and Physicians. Training is provided by authorized OncoSil Medical staff.

A.1.6 Use Environment

The OncoSil™ System is to be used in a licensed treatment facility. These facilities must hold an appropriate license for the isotope Phosphorous-32 (32P), 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.

The OncoSil™ System is prepared in a licensed Radiopharmacy or Nuclear Medicine Department.

The implantation procedure is to be conducted in a sterile-field surgical environment. The healthcare institution must support the necessary infrastructure to maintain the traceability of the device, and details of the procedure for post-market surveillance purposes. Endoscopic ultrasound (EUS) must be available for the implantation procedure and SPECT/CT imaging is advised following the implantation procedure.

A.2 Device Classification

The OncoSil™ System is classified as a Class III Active Implantable Device.

A.3 Device Description

A.3.1 Mode of Action

The OncoSil™ System is a brachytherapy device that implants a pre-determined dose of beta radiation emitting isotope directly into cancerous tissue. The beta particles emitted by the Device travel a short distance in tissue causing direct damage to cancer cell DNA, which renders them incapable of further cell division and proliferation. Through this mechanism, the Device can stop cancer cells from multiplying and ultimately shrink tumour masses when the cells eventually die.

A.3.2 Functional Description

The OncoSil™ System is comprised of Phosphorous-32 Microparticles (hereafter Microparticles) and OncoSil Diluent (hereafter Diluent). 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 Microparticles are provided in individually crimp-sealed vials, containing 250 ±10% MBq at 12:00 CET (CEST) on the reference date. Each vial is moist heat (autoclave) sterilised. Each individual vial of Microparticles is placed inside a Perspex lined lead pot to shield personnel from radiation during shipping and handling.

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

The Diluent is moist heat (autoclave) sterilised and provided in individually crimp-sealed vials each containing approximately 9 mL of Diluent.

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

The OncoSil™ System is supplied sterile and is intended for single-patient, single-use.

A.3.3 Previous Generation(s) or Variants

There are no previous generations or variants of the OncoSil™ System.

A.3.4 Description of Accessories

The OncoSil™ System does not include any 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 20-25 cm, to minimise 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, 5-7 cm 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

A.3.5 Description of other devices and products intended to be used in combination with the device

Not applicable.

A.4 Information on any residual risks and any undesirable effects, warnings and precautions

A.4.1 Residual risks and undesirable effects

Known side-effects associated with the OncoSil™ System are;

1. Procedure-related pain and/or discomfort
2. Abdominal pain and/or discomfort
3. Nausea
4. Vomiting
5. Lethargy
6. Fever
7. Abnormal liver function tests

The risk analysis has shown there is one residual intolerable risk:

- Cytotoxicity, resulting in cell/tissue death
    - This is acceptable as Microparticles are radioactive and therefore cytotoxic by design. This risk is the product's mode of action.

All other risks are either initially or through mitigations, rendered acceptable outcome.

A.4.2 Warnings

- If any signs of damage or ineffective sterile barrier integrity are observed for 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.
- OncoSil™ System is supplied sterile. There is no data to support the sterility or functionality of OncoSil™ past its expiration date.

A.4.3 Precautions

- Implantation of OncoSil™ should not occur in the following special situations:
    - Presence of multiple collateral vessels surrounding or adjacent to the target tumour
    - Presence (or significant risk) of varices near the target tumour
- Caution is advised where previous EUS (e.g. diagnostic EUS-FNA) was considered technically too difficult.
- Caution is strongly advised in the setting of recent, clinically significant pancreatitis. Implantation is not recommended.
- Chemotherapy should not be administered within 48 hours either side of the OncoSil™ implantation.
- OncoSil™ has not been studied in patients who have previously received radiotherapy to the target organ.
- 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.

- The safety of OncoSil™ has not been established in patients who are pregnant or who, within twelve months of implantation, become pregnant.
- The safety of OncoSil™ has not been established for future children of patients who are pregnant at the time of implantation, or who, within twelve months of implantation, become pregnant.
- The safety of OncoSil™ has not been established for children being breastfed by patients at the time of implantation or subsequent to implantation.
- The safety of OncoSil™ has not been established in patients who are < 18 years of age and is therefore not indicated for use in this population group.
- Due to limited clinical experience, caution is advised when treating tumours with volumes in excess of 50cc with OncoSil™. A risk-benefit assessment by the implanting physician is strongly advised.
- The device is MR Safe – the implanted device does not contain any metallic component.

A.4.4 Field Safety Corrective Actions (FSCA) and Field Safety Notices (FSN)

To date there have been no field safety corrective actions or field safety notices associated with the OncoSil™ System.

A.5 Clinical evaluation

The clinical evidence supporting this device was assessed and endorsed by the Notified Body, based upon:

1. Pre-market clinical safety studies
2. OncoSil Clinical investigations (primarily OncoPaC-1 and PanCO, as well two earlier studies DB2-201 and -202)
3. Literature search of the Device under Evaluation (Due), and the State-of-the-Art (SOTA)
4. Adverse Event/Advisory Notices Database
5. Naïve Indirect Treatment Comparison
6. Ongoing Post-Market Surveillance and Vigilance activities

A.5.1 Summary of clinical evaluations

OncoSil™, containing beta-emitting ^{32}P, has been developed as a targeted radiation treatment option for patients with unresectable, locally advanced pancreatic cancer (LAPC). Patients with advanced pancreatic cancer (both LAPC and metastatic PC) have few treatment options and a very poor prognosis. The mainstay of treatment for this group of patients is systemic chemotherapy, with a potential role for concomitant radiation therapy in selected patients.

Local disease control is an important goal of treatment in this patient group and there is a need for new and more effective locally-directed therapies. There are no approved brachytherapy devices for pancreatic cancer. Brachytherapy with OncoSil™ permits a greater radiation dose to be delivered in a highly targeted manner directly into a tumour in a single implantation, with sparing of surrounding critical organs, when compared with external beam radiation therapy (EBRT) techniques, and without the need to reduce the dose of chemotherapy while is delivered.

The treatment objective for OncoSil™ is to achieve local disease control in patients with locally advanced unresectable pancreatic cancer, which is quantified as ≥75% Local Disease Control Rate at 16 weeks (approximately 12 weeks post-implantation) in treatment-naïve patients with locally

advanced unresectable pancreatic cancer receiving first-line systemic gemcitabine-based (e.g. gemcitabine + nab-paclitaxel) chemotherapy, together with an acceptable safety profile.

Treatment with OncoSil™ in addition to chemotherapy has not been compared directly with other standard therapies in the setting of prospective randomised controlled studies. However, efficacy measures reported in the original pilot OncoSil™ clinical studies (DB2-201 and -202) in advanced pancreatic cancer confirmed the feasibility of EUS-directed implantation of the device and high LDCR of >80% when used with systemic chemotherapy (gemcitabine), based on accepted criteria of tumour response (RECIST). These disease control rates compared favourably with historical data from an appropriate alternative regimen (EBRT combined with gemcitabine chemotherapy). Treatment with OncoSil™ was-tolerated with a safety profile that also compared favourably with EBRT. Very few AEs were considered causally related to OncoSil™. Importantly, there was no evidence of serious toxicities to dose-limiting structures that may limit standard EBRT.

These findings are supported by the results of the multinational PanCO and OncoPaC-1 studies, from which safety and efficacy data obtained in 59 unresectable LAPC patients (51 implanted with the OncoSil™ device) are reported at a median follow-up of 31.6 and 27.3 months, respectively. These studies utilised the same intended intra-tumoural dose of the OncoSil™ device as the larger of the earlier pilot studies (100 Gy) but combined use of OncoSil™ with contemporary guideline-recommended first-line combination systemic chemotherapy regimens (gemcitabine + nab-paclitaxel or FOLFIRINOX).

An updated systematic literature review (SLR) provides an objective analysis of the outcomes from a broader range of prospective phase 2 and 3 studies of systemic chemotherapy (CT-only) and induction chemotherapy plus concurrent chemoradiotherapy (ICT + CCRT) regimens supported in clinical guidelines as the current state-of-the-art treatment for unresectable LAPC. The outcomes from this SLR were compared with the results of the PanCO study in a naïve indirect treatment comparison and analysed using a binomial test in compliance with the relevant Essential Requirements/General Safety and Performance Requirements from the EU MDR 2017/745 and MEDDEV 2.7\1 Rev 4 (Clinical Evaluation) for CE Marking to confirm that the OncoSil™ device, when combined with contemporary systemic chemotherapy regimens, demonstrates the following:

- Local Disease Control Rates at 16 weeks ($LDCR_{16\ weeks}$) of 82% in the Intention-to-Treat (ITT) cohort of enrolled patients and 90.5% in the Per Protocol (PP) population that received OncoSil™ plus CT, demonstrate that the PanCO study convincingly met its *a priori* primary performance endpoint ($p<0.0001$ and $p=0.0001$, respectively).
- Prolonged median overall survival (mOS) of 15.2 months in the ITT cohort and 15.5 months in the PP population, with one-year survival rates of 61.7% and 64.3%, respectively. In the naïve indirect treatment comparison, the PanCO mOS results were significantly longer ($p<0.0001$) than CT-only and ICT + CCRT regimens. These results demonstrate that treatment with OncoSil™ resulted in a 2.2 to 2.5 month increase in survival duration compared with the meta-analysis of mOS for CT-only or ICT + CCRT regimens.
- An encouraging rate of surgical resection with curative intent in nearly one in four PanCO study participants (23.8%) that received OncoSil™ plus CT, translating to 20.0% in the ITT cohort these rates were significantly greater than those reported in the CT-only and ICT + CCRT studies ($p<0.001$) and, notably, the rate of R0 margin status was 80%. Surgical resection of pancreatic cancer, particularly in patients previously determined to be unresectable, profoundly improves their prognosis from a 5-year survival rate of 5% to >20%.
- Progression-free survival (PFS) was also prolonged (9.3 months in the ITT and PP populations), and was significantly greater than 'state-of-the-art' CT-only and ICT + CCRT studies ($p=0.002$).

- Disease control and overall response rates in the PanCO study – 95.7% and 29.8%, respectively, in the ITT group; 100% and 31.0% in the PP population – underline the response following OncoSil™ administration and were again significantly greater than the CT-only and ICT + CCRT studies in the naïve indirect treatment comparison.
- There were clinically relevant and statistically significant decreases in other outcomes often not reported in clinical studies:
    - Overall, there was significant decrease in target tumour volumes (median reduction by Week 16: 38.3%, maximal median reduction 51.9%; $p<0.0001$) demonstrated evidence of target (implanted) pancreatic tumour regression.
    - Significant metabolic response on FDG-PET scanning in implanted study participants from baseline to Week 12 ($p=0.0003$ for TLG; $p<0.0001$ for SUV_{Max}) with 5 implanted study participants demonstrating complete metabolic response.
    - A significant reduction in the CA 19-9 tumour marker in implanted study participants from baseline (median maximal decrease: 82.3%; $p=0.0024$), with 81.8% of evaluable participants showing a ≥50% reduction or normalisation of CA 19-9 levels.
- These encouraging results were achieved despite relatively low CT intensity (due to dose delays ≥1 week, dose reductions and/or termination of CT) which was observed in study participants prior to OncoSil™ administration as well as in a similar proportion of the study participants who did not receive OncoSil™.
- The primary endpoint of the PanCO study was met, with the results demonstrating a satisfactory safety profile overall, with no convincing evidence of significant safety concerns or unanticipated/serious toxicities associated with the OncoSil™ investigational device and/or implantation procedure over a prolonged study timeframe.

Overall, it is considered that the OncoSil™ device provides a valuable treatment option in an area of high unmet medical need with an acceptable safety and tolerability profile. Furthermore, the clinically relevant benefits of OncoSil™ in addition to chemotherapy in appropriate patients with unresectable LAPC more than outweigh the identified risks and represent a favourable benefit-risk profile.

The safety and performance of the device as claimed has been established, and the associated device risks are more than acceptable when weighed against the benefits to the patient.

A.5.2 Overall summary of clinical performance and safety

The PanCO and OncoPaC-1 studies confirm the safety and clinical performance of the OncoSil™ device, when used in addition to contemporary systemic chemotherapy regimens.

These data demonstrate the following:

Safety

- Safety was monitored and reported in the PanCO and OncoPaC-1 study participants from enrolment through to the end of study, representing a median follow-up of 31.6 and 27.3 months, respectively.
- There were relatively few TEAEs/TESAEs that were attributed to the OncoSil™ device and/or implantation procedure compared to chemotherapy (60 *vs*. 754 attributed to chemotherapy, representing 8% vs. 63.5% of total TEAEs/TESAEs reported in the PP cohorts, respectively). Even then, two-thirds (68.3%) of the events that had possible or probable causality by the OncoSil™ device and/or implantation were also possible or probable causality by chemotherapy. In addition, it was notable that there were only 2 TEAEs/TESAEs attributed to the OncoSil™ device and/or

implantation procedure that occurred >120 days post-implant, and only 13% of the events (5 of 60) occurred in the period of >60 days post-implant.

- Very few Grade ≥3 TEAEs/TESAEs were attributed to the OncoSil™ device or implantation were experienced (15 events in 9.8% of study participants) compared to chemotherapy (96 events occurring in 70.6% of the study participants).
- Critical categories of Grade ≥3 TEAEs/TESAEs (including all events, haematological events, neutropenia, non-haematological events and GI events) peaked pre-OncoSil™ implantation compared to the monthly cycles post-implant, providing further reassurance that the OncoSil™ device is highly unlikely to be causing significant tolerability issues for study participants with LAPC receiving standard-of-care systemic chemotherapy.
- There is no evidence to suggest any negative effects from the OncoSil™ device and/or implantation procedure on the pancreas, bile duct or GI tract, or any association with biliary, duodenal, gastric or pancreatic TEAEs.
- A disproportionately high percentage of study participants (30.8%) experienced TEAEs/TESAEs in the one-month follow-up period prior to OncoSil™ device implantation compared to the 26.2–30.6 months post-implant median follow-up period (69.2%).
- The number of TESAEs were acceptable. Sixteen (16) TESAEs were reported in the cohort of eight (8) study participants who were not implanted with the OncoSil™ device, compared with 99 TESAEs in the 51 implanted study participants, representing similar proportion of events (2.0 vs. 1.9 events per study participant, respectively). Of these 99 events in the implanted cohort, 17 TESAEs occurred in 12 participants in the one-month median follow-up prior to OncoSil™ device implantation, compared to 82 TESAEs in 28 study participants in the 26.2–30.6 months median follow-up period post-implantation.

- Three (3) anticipated SADEs were reported, of which two (2; abdominal pain and neutropenic sepsis) occurred in the same study participant, were resolved and were considered possibly related to the investigational device. The third anticipated SADE involved intravasation of the OncoSil™ device in a study participant with intra-tumoural varices resulting in shunting of all implanted activity to the lung. Upon review, it was clear that the study participant did not meet the recommendations for treatment with the OncoSil™ device.
- No clinical sequelae were experienced by the study participant over a follow-up period of 10 months and Safety Review Committee recommendations to strengthen the exclusion criteria were adopted in order to mitigate the risk of such an event being repeated.
- There were no deaths that were related to the OncoSil™ device, implantation procedure or protocol chemotherapy. Pancreatic cancer was the cause of death, or contributed to the study participant's death, in all except two (2) participants, which were attributed by investigators to CVA and sepsis, the latter event in a participant who was not implanted with the OncoSil™ device.
- Serum amylase monitoring demonstrated that there was no evidence of any measurable non-target effects from the OncoSil™ device.
- Systemic circulation of low levels of ^{32}P activity peaked at 7–14 days post-implant in urine and day 21 in blood, representing less than 0.5% of implanted activity. The principle non-target organs exposed to the radioactivity were the kidneys and urinary bladder wall. Assuming that the maximal activity of OncoSil™ was implanted, the kidneys and urinary bladder wall would receive a maximum absorbed dose of 0.013 and 0.48 mGy, respectively. These absorbed doses represent clinically trivial exposure, as the generally accepted tolerance dose to these organs is 20 Gy. There was no evidence of any associated radiological toxicities.

- Evidence of the utility of contemporary SPECT/CT Bremsstrahlung imaging for confirming satisfactory localisation of the OncoSil™ device following implantation.
- User experience confirms the feasibility, acceptability and tolerability of EUS-directed implantation. It is recognised there is a 'learning curve' amongst operators given the novelty of the therapy. It is anticipated that as greater experience is obtained over time, adjustments and enhancements to the procedure should result in further optimisation of implantation.

The safety data from the PanCO and OncoPaC-1 studies also confirm the safety and tolerability from the earlier DB2-201 and DB2-202 studies in participants with advanced pancreatic cancer.

There is no evidence to suggest significant additional risk when the OncoSil™ device is used in addition to contemporary systemic chemotherapy regimens. The overall safety profile is consistent with that expected in a high-risk population receiving multi-agent chemotherapy. The acceptability of the current safety profile has been confirmed by the two independent SRCs which met on 9 occasions to scrutinise the accumulating safety dataset.

Clinical Performance

- The results of the PanCO and OncoPaC-1 studies, at median follow-up intervals 31.6 and 27.3 months, respectively, provide a broad and consistently positive set of outcomes that underline the clinically relevant benefits that treatment using the OncoSil™ device in combination with contemporary systemic chemotherapy regimens, provide for patients with unresectable LAPC:

- The PanCO study met and exceeded the *a priori* primary performance endpoint of $LDCR_{16\ weeks}$, demonstrating effective local disease control (82.0% in the ITT population, p=0.0001; 90.5% in the PP population, p<0.0001).
- The studies reported prolonged Overall Survival (OS) following OncoSil™ in addition to chemotherapy, with a median OS of 15.5 months in the PP population (15.2 months ITT) and 27.3 months in the OncoPaC-1 ITT population.
- These OS data were further confirmed by the Progression-Free Survival (PFS), which was 9.3 months in both PanCO populations and 12.2 months in the OncoPaC-1 ITT population. Local PFS (LPFS) was 9.9 and 9.8 months, respectively, in the PanCO ITT and PP populations, and 27.3 months in the OncoPaC-1 ITT population.
- Nearly one-in-four PanCO study participants (23.8%) receiving OncoSil™ subsequently underwent surgical resection with curative intent, 80% had R0 margins. This had a profound improvement in participants' prognosis with 6 alive (5 disease-free) 26.4–35.3 months from enrolment. The qualitative surgical experience suggests that patients treated with the OncoSil™ device plus chemotherapy may be easier to resect than those treated with EBRT. The OncoSil™ mode of action may play an important role in contributing to this. The morbidity was in line with surgical experience, while the 180-day mortality rate post-resection was 0%. This promising finding indicates the potential to 'convert' patients with LAPC from initially inoperable to a surgically resectable and potentially curative state when the OncoSil™ device is added to standard-of-care chemotherapy.
- The Disease Control Rate (DCR) in implanted study participants was 100% in the PanCO and OncoPaC-1 studies, and 95.7% in the PanCO ITT population, with an Overall Response Rate (ORR) 29.8% and 31.0% in the PanCO ITT and PP populations, respectively, and 22.2% in the OncoPaC-1 study. These further underline the response to treatment with OncoSil™ and standard-of-care chemotherapy.

- Evidence of clinically relevant target (implanted) pancreatic tumour regression, with statistically significant and many cases substantial volumetric reduction (mean reduction of -38% by Week 16, maximum reduction 90%; p<0.0001, and -52% at best response).
- There was a substantial metabolic response on FDG-PET scanning in implanted study participants from baseline to Week 12, with 5 participants demonstrating complete (100%) metabolic response.
- There was also evidence of significant reduction in the CA 19-9 tumour marker in implanted study participants from baseline to Week 16 (*p*=0.0082) with 81.8% of the PanCO PP population having a clinically relevant normalisation or ³50% reduction in CA 19-9 levels, and 36.4% of evaluable participants showing a reduction in CA 19-9 of ³90%.
- These encouraging results were achieved despite relatively low chemotherapy intensity (dose delays ³1 week, dose reductions and/or termination of chemotherapy), which was seen in study participants prior to OncoSil™ device administration as well as in a similar proportion of the study participants who did not receive OncoSil™.

The results from the PanCO and OncoPaC-1 studies provide a broad and consistently positive set of clinical performance outcome measures that underline the clinical benefits that treatment with OncoSil™ provides for patients with unresectable LAPC.

A.5.2.1 Documented Clinical Benefits

The OncoSil™ device, when combined with contemporary systemic chemotherapy regimens, demonstrates the following:

- Local Disease Control Rates at 16 weeks ($LDCR_{16\ weeks}$) of 82% in the Intention-to-Treat (ITT) cohort of enrolled patients and 90.5% in the Per Protocol (PP) population that received OncoSil™ plus CT, demonstrate that the PanCO study convincingly met its *a priori* primary performance endpoint ($p<0.0001$ and $p=0.0001$, respectively).
- Prolonged median overall survival (mOS) of 15.2 months in the ITT cohort and 15.5 months in the PP population, with one-year survival rates of 61.7% and 64.3%, respectively. In the naïve indirect treatment comparison, the PanCO mOS results were significantly longer ($p<0.0001$) than CT-only and ICT + CCRT regimens. These results demonstrate that treatment with OncoSil™ resulted in a 2.2 to 2.5 month increase in survival duration compared with the meta-analysis of mOS for CT-only or ICT + CCRT regimens.
- An encouraging rate of surgical resection with curative intent in nearly one in four PanCO study participants (23.8%) that received OncoSil™ plus CT, translating to 20.0% in the ITT cohort these rates were significantly greater than those reported in the CT-only and ICT + CCRT studies ($p<0.001$) and, notably, the rate of R0 margin status was 80%. Surgical resection of pancreatic cancer, particularly in patients previously determined to be unresectable, profoundly improves their prognosis from a 5-year survival rate of 5% to >20%.
- Progression-free survival (PFS) was also prolonged (9.3 months in the ITT and PP populations), and was significantly greater than 'state-of-the-art' CT-only and ICT + CCRT studies ($p=0.002$).
- Disease control and overall response rates in the PanCO study – 95.7% and 29.8%, respectively, in the ITT group; 100% and 31.0% in the PP population – underline the response following OncoSil™ administration and were again significantly greater than the CT-only and ICT + CCRT studies in the naïve indirect treatment comparison.
- There were clinically relevant and statistically significant decreases in other outcomes often not reported in clinical studies:
    - Overall, there was significant decrease in target tumour volumes (median reduction by Week 16: 38.3%, maximal median reduction 51.9%; $p<0.0001$) demonstrated evidence of target (implanted) pancreatic tumour regression.
    - Significant metabolic response on FDG-PET scanning in implanted study participants from baseline to Week 12 ($p=0.0003$ for TLG; $p<0.0001$ for SUV_{Max}) with 5 implanted study participants demonstrating complete metabolic response.
    - A significant reduction in the CA 19-9 tumour marker in implanted study participants from baseline (median maximal decrease: -82.3%; $p=0.0024$), with 81.8% of evaluable participants showing a ^{3}50% reduction or normalisation of CA 19-9 levels.
- These encouraging results were achieved despite relatively low CT intensity (due to dose delays ^{3}one week, dose reductions and/or termination of CT) which was observed in study participants prior to OncoSil™ administration as well as in a similar proportion of the study participants who did not receive OncoSil™.

A.5.2.2 Benefit-risk assessment

Treatment options for LAPC remain limited. Currently, surgical resection with curative intent remains a cornerstone treatment for LAPC, providing the greatest likelihood of long-term survival. However, major surgery inherently carries risks, and patient quality of life and anticipated recovery following surgery are considerations in any surgical procedure. There is also the risk that subsequent treatment options are more limited if early recurrence occurs after resection. However, the potential for cure outweighs these risks, and surgical resection is widely supported by clinical guidelines.

Chemotherapy and chemoradiotherapy remain the standard of care where surgical resection is not possible, to improve survival outcomes and to provide local disease control. These treatments also offer flexibility; clinical evidence has demonstrated an impact of chemotherapy on survival outcomes when used as first line therapies or as consolidation therapy following successful induction therapy. In addition, neoadjuvant chemotherapy or chemoradiotherapy has the potential to downstage disease allowing for conversion surgery in some patients. However, these therapies are burdensome and morbidity rates can be high, particularly when considering multi-agent regimens and the high potential for co-morbidities in patients with LAPC. Both chemotherapy alone and chemoradiotherapy are supported by clinical guidelines, but there is still debate around optimum treatment regimens and whether chemoradiotherapy provides survival benefit over chemotherapy. Furthermore, despite clinical recommendations for the use of chemotherapy and chemoradiotherapy in LAPC, the bulk of data stems from trials in patients with metastatic PDAC.

Several other therapies have been assessed in clinical studies, and are used as treatments for unresectable LAPC that are not currently supported by clinical guidelines. Brachytherapy is a highly targeted therapy which benefits from causing minimal damage to surrounding tissues and can provide a treatment alternative to patients with chemo-intolerance. However, more data and optimization/standardization of protocols and procedures are required. Ablative therapies offer various options in terms of route of administration so can be minimally invasive. While IRE can be used to target malignancies adjacent to vital structures, thermal ablative techniques (RFA and MWA) risk damage to surrounding tissues. When used in combination with chemotherapy or chemoradiotherapy, these approaches may offer potential for synergistic efficacy to improve outcomes, but morbidity associated with these procedures may be restrictive. Overall, currently available data are insubstantial to recommend these therapies in clinical practice and prospective, randomized, controlled trials are warranted.

A.5.3 Post-Market Clinical Follow-ups

The PMCF programme entails several methods that are being used to proactively capture and evaluate clinical data of the OncoSil™ device after it has been placed on the market. The aim of the programme is to confirm the safety and performance throughout the expected lifetime of the device and ensuring the continued acceptability of identified risks and detect emerging risks on the basis of factual evidence.

Sources of evidence are the evaluation of spontaneous reports, the interrogation of Adverse Event databases and clinical study databases. A post market clinical follow-up registry has been initiated to actively capturing safety and efficacy data on patients in the UK and the EU who are treated in a post-market commercial setting. Safety data is also reported through investigator-initiated clinical studies.

An active clinical development program comprises of additional studies that will generate further safety and efficacy data to broaden the clinical evidence and potentially expand the indications for use.

A.5.4 Possible Therapeutic Alternatives

Surgical resection is the only effective treatment approach for a potential chance of cure and long-term survival in patients with pancreatic cancer. Only 15–20% of patients present with a surgically resectable tumours; in patients with initially unresectable LAPC, conversion surgery is an option, whereby chemotherapy with or without radiotherapy are used to shrink the tumour tissue sufficiently to allow surgery. When surgical resection is not an option, chemotherapy with or without chemoradiotherapy is the standard of care. Recommended first-line chemotherapy regimens include gemcitabine alone, gemcitabine plus nab-paclitaxel (Gem/Nab-P), other gemcitabine-based combination chemotherapy, and FOLFIRINOX. While these regimens provide reasonable OS and PFS, much of the prospective data that informs guidelines is from trials that included patients with borderline resectable LAPC or metastatic pancreatic cancer. Data on the addition of radiotherapy to chemotherapy are mixed, with some studies showing a benefit of the combination, whilst recent larger-scale trials have been less positive. Other treatment options for unresectable LAPC include brachytherapy, irreversible electroporation (IRE), and ablation. There are advantages and disadvantages to all of these treatment options. For example, all these treatments are associated with morbidity, whilst surgical resection, ablation and IRE are associated with a (low) risk of mortality. Therefore, there remains an unmet need for newer treatment options with better safety and efficacy profiles for the treatment of unresectable LAPC.

Note: There is no device equivalent to the OncoSil™ System.

A.6 Suggested Profile and Training for Users

The OncoSil™ System is intended to be used only by Radiopharmacists, Nuclear Medicine Personnel and Physicians. Training is provided by authorized OncoSil Medical staff.

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 Programme:

- 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)

Two separate training courses are provided by OncoSil:

1. **Authorised Dispensers (AD)** - the person preparing the OncoSil™ suspension (i.e. Radiopharmacist, Nuclear Medicine Personnel):
2. **Authorised User (AU)** - the physician physically depressing the syringe containing OncoSil™ during the implantation procedure. The AU training involves.
    a. Performing their first patient implantation supervised by an OncoSil Medical representative (Authorised 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 Programmes in order to be accredited in both roles.

A.7 List of Harmonised Standards

A list of technical standards to which OncoSil Medical Ltd. comply with to demonstrate compliance with the Essential Requirements of Safety and Performance are provided in document REG_OS01_COMM_P_GLO_EN_005 Version 1_Standards List

Appendix B This section is intended for Patients

Download the latest version of this document here
https://www.oncosil.com/patients/

B.1 Device Purpose and Action

- OncoSil™ is a medical device, which has been on the market since 2020 for the treatment of people with pancreatic cancer. There is currently no similar medical device available.
- OncoSil™ consists of particles that carry the active treatment "radioactive Phosphorous (P-32)".
- These particles are tiny, and range in diameter from 28 to 32 micrometres, which is smaller than the width of a human hair (which typically ranges in width from 40 to 120 micrometres).
- The particles carrying P-32 are injected (or implanted) directly into the tumour in the pancreas.
- The implantation is carried out using a long thin tube with a camera inside (endoscope), which is guided by ultrasound down the throat into the stomach and the first part of the small intestine (duodenum).
- Once implanted, the OncoSil™ particles will remain permanently in your tumour and this has been tested for long-term safety.
- The particles have a radioactive half-life of 14.7 days (which means the radioactivity falls to half in this time and continues to fall over time – to about 2% of the initial activity after 81 days). The particles are considered a permanent implant. The OncoSil™ device is used to deliver radiation from P-32 directly into your tumour to destroy cancer cells.

Intended Purpose

- The OncoSil™ System is intended to prevent further growth of the tumour and reduce tumour size in people with pancreatic cancer that cannot be managed with surgery and has grown outside the pancreas but has not spread to other parts of the body (so-called inoperable locally advanced disease).
- OncoSil™ is used in people who are also receiving chemotherapy (specifically gemcitabine-containing chemotherapy), by implantation of the radioactive P-32 particles into tumours in the pancreas using an ultrasound-guided endoscope.

Conditions treated with OncoSil™ (Indications For Use)

- OncoSil™ is used for the treatment of patients with inoperable locally advanced pancreatic cancer, in addition to standard of care chemotherapy.

Clinical Goal

- The goal of OncoSil™ treatment is to prevent growth of the tumour and reduce the size of the tumour.
- This is achieved by implanting radioactive P-32 particles into tumours in the pancreas using an ultrasound-guided endoscope.
- This delivers high doses of radiation to the tumour.
- The potential benefits to people with pancreatic cancer receiving the device are:
  - Stopping or slowing the growth of their tumour so that people live for longer without their disease worsening.
  - Reduction in size of their tumour to allow surgical removal of the tumour.

Summary of Clinical Evidence

- Researchers have tested the OncoSil™ device in 4 clinical studies in people with inoperable advanced pancreatic cancer.
- In these studies, people had cancer that was too advanced for surgical removal.
- The results of these studies showed that the side effects of the OncoSil™ device, and the procedure to implant it, were not common and usually mild.
  The people in these clinical studies were treated with OncoSil™ and chemotherapy drugs (usually consisting of gemcitabine, often combined with nab-paclitaxel).
- The most recent and most important study, which led to approval of OncoSil™, by the authorities was conducted in hospitals in Australia, Belgium and the UK.
- 50 people with inoperable locally advanced pancreatic cancer initially took part in the study, and 42 were implanted with the OncoSil™ device.
- Most people in this study had a decrease in their tumour volume over time after implantation and their disease did not worsen in the 3 months after implantation.
- In nearly a quarter of those who had OncoSil™ implanted, their tumour shrunk enough to make surgical removal possible.
- The side effects thought to have been caused by the device or the implantation process were generally mild.
- Side effects included pain or discomfort in the abdomen, pain related to the procedure (such as a sore throat), nausea, vomiting, tiredness (fatigue) or a lack of energy (lethargy), fever and abnormal results from tests that measure how the liver is working.
- The OncoSil™ device is now being used in practice, and so healthcare professionals continue to gather information on the safety and performance of the device. This information is gathered and stored in a registry.
- The information from this registry, and any other complaints or side effects reported by healthcare workers, are regularly reported to the authorities to make sure the safety and performance of the device is maintained at expected levels.
- The people included in the registry can be assessed for a longer time than those in the clinical studies and this helps to see if there are any lasting effects or issues with the device.

Risk-Benefit Assessment of Treatment with OncoSil™

- Based on the results of the clinical studies, expert authorities conclude that the OncoSil™ device has an acceptable number and severity of side effects, and the potential benefits of treatment in people with inoperable locally advanced pancreatic cancer receiving chemotherapy that includes gemcitabine outweigh the potential risks.
- They conclude that the device provides a favourable benefit-risk profile.

B.2 Possible side-effects related to any part of this treatment

- Medical treatments often cause side effects. You may have none, some or all of the side effects listed below, and they may be mild, moderate or severe.
- If you have any of these side effects, or if you would like more information about side effects and risks of this treatment, please ask your doctor.

B.2.1 Implantation Procedure

- Like other endoscopy procedures, ultrasound -guided endoscopy usually has few complications. However, potential risks include:
  - Pain, fever, feeling sick and dizzy or faint, bloating and/or a sore throat may occur, however these symptoms are usually short-lived and easily treated.
  - Side effects related to medicines used as part of the procedure such as the sedative or anaesthetic.
  - Incorrect placement of OncoSil™ particles.
  - Uncommon or rare complications of an endoscopy include bleeding or a tear of the stomach or part of the intestine (duodenum). In addition, with the insertion of a needle into the pancreas, there is a small risk of bleeding, infection or inflammation (known as pancreatitis).
  - Following treatment with OncoSil™, some radioactivity may be detected in stools or in the blood and urine. These amounts are small and have not been found to cause harm.

B.2.2 OncoSil™ Device

- OncoSil™ has been tested when added to chemotherapy in clinical studies in people with pancreatic cancer.
- Researchers thought that most side effects were due to either chemotherapy or cancer.
- However, those side effects that were possibly or probably related to OncoSil™ treatment and/or the endoscopy procedure included:
  - Fatigue or tiredness
  - Pain or discomfort in the abdomen
  - Stomach or intestine related effects – in particular, sickness, indigestion and reflux
  - Abnormal blood results – in particular, reduced white blood cells and platelets in the blood.
- The researchers involved in the studies noted that two-thirds (66%) of these side effects could also have been caused by chemotherapy, therefore it is not easy to know whether these side effects were directly related to OncoSil™ treatment.
- There is also the very small risk of accidental radiation damage to nearby normal tissue, such as the pancreas, the stomach, small intestine and large intestine, due to the OncoSil™ implant.
- Potential late radiation side effects could include:
  - Damage in the lower intestine (bowel ulceration),
  - Irritation of the lining of the stomach or intestines (enteritis),
  - Swelling of the lining of the lungs (pleurisy),
  - Swelling of the lungs (radiation pneumonitis),
  - Bleeding in the stomach or intestine,
  - Formation of a passage within body tissue (fistula),
  - Abnormal narrowing of a passage within the body (stricture).
- Treatment with OncoSil™ will add to your overall lifetime exposure to radiation. Exposure to radiation over a long time may be linked with a higher risk of cancer.
- However, the information gained to date suggests that the risk of this happening is very small.

- If unexpected complications related to the OncoSil™ radiation treatment arise, there is also a possibility that the doctor will lower the doses of chemotherapy.
- There may be other side effects or discomforts from the OncoSil™ implantation which are not yet known.

B.2.3 Chemotherapy

- OncoSil™ is added to chemotherapy. Like other medicines that treat cancer, the chemotherapy you receive may have unwanted side effects, some of which may be serious.
- You may need medical treatment if you get some of thse side effects. For more information about side effects and risks of chemotherapy, please ask your doctor.

B.3 Possible side-effects related to the interactions with other medicines you are taking at the same time (concomitant medicines)

- The safety of OncoSil™ has not been confirmed when used with other medicines, apart from certain chemotherapy drugs (gemcitabine + nab-paclitaxel [Abraxane®]).
- If you are taking other medicines at the same time you are to receive OncoSil™, you should discuss this with your doctor.

B.4 Radiation considerations following OncoSil™ implantation

- The radiation will only travel a short distance (i.e. and average of 2.76 mm or 0.11 inches, and a maximum of 8.2 mm or 0.32 inches) inside your tumour and therefore very little radiation will leave your body.
- While this is not a radiation hazard to your family or members of the public, there may be a small amount of radiation present in your urine, blood or stools.
- Therefore there are important safety practices listed below that you should follow:

B.4.1 General Interactions (for 2 weeks following OncoSil™ treatment)

- Groups vulnerable to radiation exposure, such as pregnant women, infants and children, should avoid unnecessary contact with the patient for 2 weeks.

B.4.2 Bathroom Use (for 2 weeks following OncoSil™ treatment)

- Flush the toilet twice after use.
- Wipe toilet seat and handle with a disinfecting wipe (Clorox or similar) folding it inside itself, so that used sections are covered.
- Wash your hands thoroughly with soap and warm water.

B.4.3 General Clean Up (for 2 weeks following OncoSil™ treatment)

- If any spills of bodily fluids occur, promptly clean up wearing disposable gloves.
- Place gloves and all articles used in the clean-up in a bag and dispose of them in normal household waste.
- If any bodily fluids transfer to clothing or bottom of shoes, promptly wash them separately.
- Continue these practices for a period of two weeks after an OncoSil™ treatment.

B.5 Other considerations following OncoSil™ implantation

B.5.1 Intimacy

- The safety of OncoSil™ has not been confirmed in patients who are pregnant or who, become pregnant within 12 months of implantation.
- The safety of OncoSil™ has not been confirmed for future children of patients who are pregnant at the time of implantation, or who, become pregnant within 12 months of implantation.
- Therefore, the use of contraception by both females and males who receive OncoSil™ is recommended for a period of 12 months following the OncoSil™ procedure.

B.5.2 Breastfeeding

- The safety of OncoSil™ has not been confirmed in children being breastfed by people at the time of implantation or after implantation.
- Therefore, it is recommended that people do not breastfeed for a period of at least 12 months following an OncoSil™ procedure.

B.5.3 Other Medical Procedures

- Upon release, people who receive OncoSil™ are provided with a small card outlining the OncoSil™ treatment, which they should keep on their person for 3 months to explain the procedure to any other healthcare professional who may need this information.
- For other appointments (such as pathology, imaging, dental, etc., or any invasive procedures) made within 3 months of OncoSil™ treatment, please ensure you inform the healthcare professional of your OncoSil™ implant when booking your appointment.
- If you require extra care or support with your day-to-day activities, following your OncoSil™ implantation, then please discuss this with your physician.
- The device is MR Safe – the implanted device does not contain any metallic component.

B.5.4 In the event of death within 3 months of the OncoSil™ implant

- In the event of death within 3 months of your OncoSil™ treatment, a family member should advise your doctor.
- Your doctor should contact the Coroner and provide contact details of the Radiation Safety Officer at the hospital.

4 Revision History

Revision #	Date of Revision	Description of main changes	Language validated in
0	21 December 2022	Not Applicable	English
1	15 February 2023	Re-instated the word 'locally' per the IFU	English
2	21 December 2023	Added Clinical Benefit Updated to legal manufacturers new address	English
3	8 March 2024	Updated Intended Purpose Updated Indications For Use Updated Patient Information to include history and clinical data on the device Added Revision History	English
4	30 April 2024	Updated the details of the BASIC UDI in section 3. Section A.5.1 has been updated to include the words 'locally and unresectable'.	English
5	1 Nov 2024	Added QR code links to oncosil.com website for updates to this document Added note MR Safe	English