

Summary of Safety and Clinical Performance

for

Precipitating Hydrophobic Injectable Liquid

PHIL™ System

SSCP23-0016

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DOCUMENT CHANGE HISTORY

SSCP Revision	Change Description	NB approved/verified
A	Initial release	☒Yes ☐ No* Validation language: English
B	This revision reflects latest clinical data from published literature, post-market surveillance, and post-market clinical investigations input from Regulatory, R&D, and Quality. Any other changes are made to: • Section 1.1-Device Identification and General Information: GMDN Code • Section 1.2-Intended Purpose of the Device • Section 1.3-Device Description • Section 1.4-Risks and Warnings • Section 1.5-Summary of the Clinical Evaluation and PMCF • Section 1.6-Possible Diagnostic or Therapeutic Alternatives • Section 1.8-References to any Harmonized Standards and CS • Section 1.9-References	☐Yes ☒ No* Validation language

*Annual entries must be included. An entry stating such must be added if a revision is not required.

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1 SUMMARY OF SAFETY AND CLINICAL PERFORMANCE

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions For Use (IFU) as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

1.1 Device Identification and General Information

Table 1.1 Device Identification and General Information

Device Names	
Device Trade Name	Precipitating Hydrophobic Injectable Liquid (PHIL) Liquid Embolic System
EMDN Code	C010402020302 Embolization Fluids
Medical Device Nomenclature (GMDN)	60939- Neurovascular embolization plug
Device Class	III
Basic UDI-DI	37015174PHILKC
Year when first certificate (CE) was issued for the device	2014
Legal Manufacturer	
Name & Address	**MicroVention Europe SARL (MVE)** 30 bis, rue du Vieil Abreuvoir 78100 Saint Germain-en-Laye, France
Manufacturer SRN	MVE: FR-MF-000004449
Notified Body	
Name & Address	DQS Medizinprodukte GmbH August-Schanz-Straße 21 D-60433 Frankfurt am Main Germany
Notified Body Identification Number	0297

1.2 Intended Purpose of the Device

Table 1.2 Intended Use

Intended Purpose	
Intended Purpose	The PHIL device is intended for use in the embolization of lesions in the peripheral and neurovasculature, including arteriovenous malformations and hypervascular tumors.
Indications for Use	The PHIL device is intended for use in the embolization of lesions in the peripheral and neurovasculature, including arteriovenous malformations and hypervascular tumors.

Target Population	Endovascular embolization using the PHIL device can be used in a wide range of procedures for patients requiring embolization of neurovascular or peripheral vascular lesions such as brain arteriovenous malformations (bAVMs), dural arteriovenous fistulas (dAVFs), peripheral AVMs (e.g., pulmonary AVM), peripheral AVFs, pseudoaneurysms, chronic subdural hematoma (cSDH), and hypervascular tumors.
Contraindications and/or Limitations	The use of the PHIL device is contraindicated when any of the following conditions exist: • When patient has severe iodine allergy. • When optimal microcatheter placement is not possible. • When provocative testing indicates intolerance to the occlusion procedure. • When vasospasm stops blood flow. • Not for use with premature infants (<1,500 g) or individuals with significant liver and kidney function impairment.

1.3 Device Description

Table 1.3 Device Description

<table>
<tr><th colspan="2">Device Description</th></tr>
<tr><td>Description of the Device</td><td>PHIL Liquid Embolic System is a non-adhesive liquid embolic agent made of a co-polymer dissolved in DMSO (Dimethyl Sulfoxide). An iodine component is chemically bonded to the co polymer for radiopacity purpose during injection. PHIL is an implantable device with direct intravascular tissue and blood contact for permanent patient contact duration (> 30 days).
<table>
<tr><th>Catalog Number</th><th>Concentration</th></tr>
<tr><td>LEN10250</td><td>PHIL 25%</td></tr>
<tr><td>LEN10250RE</td><td>REPHIL 25% (Refill Kit)</td></tr>
<tr><td>LEN10300</td><td>PHIL 30%</td></tr>
<tr><td>LEN10300RE</td><td>REPHIL 30% (Refill Kit)</td></tr>
<tr><td>LEN10350</td><td>PHIL 35%</td></tr>
<tr><td>LEN10350RE</td><td>REPHIL 35% (Refill Kit)</td></tr>
<tr><td>LEN10LV250</td><td>PHIL LV</td></tr>
<tr><td>LEN10LV250RE</td><td>REPHIL LV (Refill Kit)</td></tr>
</table></td></tr>
<tr><td>Design Characteristics of the Device</td><td>PHIL is a co-polymer dissolved in DMSO with an iodine component that is chemically bonded to the co-polymer to provide fluoroscopic visualization. The PHIL device is delivered in liquid phase through a DMSO primed microcatheter placed at the target lesion under fluoroscopic control. The mode of action of the copolymer is its solubility in DMSO, but insolubility in an aqueous environment. The DMSO solvent dissipates into the blood, causing the polymer to precipitate in situ into a coherent embolus. The PHIL device immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while traveling more distally in the fistulous lesion. The distance traveled before solidifying within the vasculature will depend on a number of factors, including the flow rate in the vessel, the rate of injection, and embolic agent percentage (PHIL 25%, 30%, 35%, or PHIL LV). All concentrations will complete solidification within three minutes. The PHIL 25%, 30%, 35%, and PHIL LV concentrations are available and are recommended for the following circumstances. A table below details the materials of the key functional elements of the PHIL device, and those making either direct or indirect contact with the human body. The PHIL Embolic System does not incorporate a medicinal substance, animal tissues or blood products.
<table>
<tr><th>Key Functional Element</th><th>Component</th><th>Material</th><th>Patient Contact</th></tr>
<tr><td>Flushing Solution</td><td>DMSO</td><td>Dimethyl sulfoxide (DMSO)</td><td>Direct</td></tr>
<tr><td>PHIL Embolic Liquid</td><td>PHIL co-polymer</td><td>Poly-lactide-co-glycolide (PLGA) and Hydroxyethyl methacrylate (HEMA) dissolved in DMSO</td><td>Direct</td></tr>
<tr><td>Syringe</td><td>Barrel</td><td>Borosilicate glass</td><td>Indirect</td></tr>
</table></td></tr>
</table>

			Luer	Stainless Steel 316/316L	Indirect
			Stopper	Ethylene propylene diene monomer	Indirect
			Plunger	Stainless Steel 304	Indirect
			Cap	Polypropylene	Indirect
			Finger grip	Polypropylene (yellow or white)	No contact
		Universal Adaptor	Hub	Polypropylene, 304/304L Stainless Steel	Indirect
			Tuohy Borst Body	Polypropylene	Indirect
			Tuohy Borst Cap	Polypropylene	No contact
			Tuohy Gasket	Silicone	No contact
		Tray Packaging	Tray	Polycarbonate	No contact
			Tray Lid	Tyvek	No contact
			Insert	Solid Bleached Sulfate Paperboard	No contact
			Carton	Solid Bleached Sulfate Paperboard	No contact
Previous Generations or Variants, if applicable	There are no prior versions of the PHIL device.				
Single use – sterilization method	The PHIL liquid embolic system is packaged sterile, for single use only. The device is sterilized with moist heat (steam sterilization) and the packaging is intended to protect the device through its shelf life.				
Description of Accessories	The universal adaptor is intended for use as an accessory to the PHIL. The use of the adaptor minimizes mixing (dilution of) the Liquid Embolic solution as it leaves the syringe while also serving to connect the syringe to the microcatheter. The proximal end of the adaptor is connected to the syringe. The distal end of the adaptor has a universal design allowing connection to most commonly used microcatheters. One adaptor per liquid polymer syringe is required. The adaptor is attached to the end of the syringe and the tip of the adaptor tube is positioned within the hub inner diameter to minimize mixing of DMSO within the hub to prevent dilution of the liquid embolic when delivered through the microcatheter and minimize the dead space.				
Description of other Devices or Products intended to be used in combination	• Platinum coils may be used to effectively slow the flow, thus facilitating the following embolization with a liquid embolic agent. • Microcatheters/Catheters, especially the recently developed detachable tip microcatheters/catheters have facilitated the removal of the catheter from hardened liquid embolic casts. • Balloon microcatheters/catheters are used to enhance the protection of normal vasculature and improve the penetration of liquid embolics into large bAVMs/AVMs, which led to a reduction in the procedure times and radiation exposure. In particular, a dual-lumen balloon microcatheter (such as the Scepter Mini) may allow a more efficient and controlled injection of liquid embolic agents in smaller, more distal arteries (>1.7 mm), thereby reducing risks of reflux.				

1.4 Risks and Warnings

1.4.1 Residual Risks and Undesirable Effects

Hazards associated with the use of the PHIL Liquid Embolic System are assessed and risks of the resulting harms are minimized through the use of risk mitigation/control measures. All known foreseeable risks have been evaluated and mitigated.

Risks associated with the PHIL Liquid Embolic System include the following:

- Device not biocompatible or not sterile; packaging failure
- Dimethyl Sulfoxide (DMSO) introduce too quickly
- Liquid embolic migrate outside of targeted area due to misuse of product
- Device used after expiration date
- Device used outside of the intended use / Off label use of device,exposure to liquid embolic material for unintended application and/or population (patient), which may result in catastrophic health effects, including death. Unable to inject Liquid Embolic material to operate intended area due to Liquid Embolic material occlusion in catheter lumen
- Unable to inject Liquid Embolic material into microcatheter due to device contamination from waste products and or medical device disposal
- Catheter breakage or rupture due to improper use of catheter, excessive pressure to inject liquid embolic material, or incompatibility of catheter
- Product is an irritant to vessel and/or patient intolerability
- Improper anticoagulation or catheter degradation during procedure
- Lack of cohesive/consistency of product or foreign body embolism due to incorrect formulation
- Catheter entrapment or difficult to remove catheter due to vasospasm; product reflux or very distal afferent; lengthened and tortuous pedicle
- Inadequate visibility under fluoroscopy incorrect PHIL device deployment due to incorrect formulation or material selection
- PHIL liquid changes to a brown / dark color due to exposure to higher temperature than suggested

Across published clinical literature, within follow-up periods ranging from 45 days to 12 months, reported complication rates included: mortality 0%–40%, stroke 1.0%–9.1%, cranial-nerve deficits 3.1%–6.3%, permanent neurological complications 3.7%–4.2%, and overall morbidity 3.9%–4.3%. Hemorrhagic events comprised overall hemorrhage 13.9%, subarachnoid hemorrhage 5.6%–9.1%, hematoma 8.3%, delayed hemorrhage 9.1%, and intracranial hemorrhage 3.7%. Ischemic events were reported at 11.1%. Device- and access-related events included microcatheter retention 0%–9.1%, embolic/venous migration or fragmentation 2.8%–3.9%, perforation 2.8%, air embolus 1.3%, and vasospasm 12.5%, and reflux without sequelae 16.7%; recurrence was low (2.1%) where explicitly measured, and multiple cohorts reported no complications.

1.4.2 Warnings and Precautions

The warnings and precautions for the PHIL device are:

Warnings

- Performing embolization to occlude blood vessels is a high-risk procedure. This device should be used only by physicians with neuro or peripheral interventional training and a thorough knowledge of the vascular pathology to be treated, vascular architecture, angiographic techniques, and super-selective embolization techniques.
- Vascular malformation embolization may influence or change blood flow patterns, thereby subjecting arteries supplying the vascular malformation or the normal surrounding tissues and perivascular space around the malformation to increased pressures, or by causing an increase in the intra-nidal pressure. These conditions could result in hemorrhagic complications.
- Care must be taken to avoid venous outflow occlusion prior to nidal or arterial feeders as this may also produce malformation hemorrhage. If the PHIL device extravasates outside the vascular space, secondary to vessel wall compromise, a sub-acute inflammatory response to the material may occur in the surrounding vascular space which may lead to tissue damage.
- There may be some topical hypersensitivity and/or release of histamines from Dimethyl Sulfoxide (DMSO).
- Therapeutic embolization should not be performed when high blood flow precludes safe delivery of the embolic agent to prevent non-target embolization.
- **The microcatheter tip should be placed as distal as possible, and as close to the target vascular lesion as possible to prevent any non-target embolization of normal surrounding tissue or cranial nerves.**
- Premature solidification of the PHIL device may occur if the microcatheter or luer hub comes in contact with any solution such as saline, blood or contrast.
- Use only DMSO compatible microcatheters indicated for use in the neuro or peripheral vasculature. Other microcatheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to microcatheter degradation.
- Use only the MicroVention pre-filled syringes to inject DMSO and the PHIL device. Other syringes may not be compatible with DMSO.
- Rapid injection of DMSO into the vasculature space may lead to vasospasm and/or angionecrosis.
- In the event of microcatheter occlusion, excessive force to advance the plunger may result in microcatheter rupture due to over pressurization.
- Do not allow more than **1 cm of the PHIL device** to reflux back over microcatheter tip. Excessive reflux may result in difficult microcatheter removal.

- After using a microcatheter with the PHIL device, do not attempt to clear or inject any material through it. Such attempts may lead to embolus or non-target embolization.
- STOP injection if the PHIL device is not visualized exiting the microcatheter tip. If the microcatheter becomes occluded, over-pressurization and vessel rupture can occur. During injection, continuously verify under fluoroscopy that the PHIL device is exiting the microcatheter tip.
- STOP injection if increased resistance is observed. If increased resistance occurs, determine the cause (e.g. occlusion in microcatheter lumen) and replace the microcatheter if needed. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in microcatheter or vessel rupture and embolization of non-target areas.
- Only use thumb pressure to inject the PHIL device. Using the palm of hand to advance plunger may result in microcatheter or vessel rupture due to over pressurization in the event of microcatheter occlusion.
- DO NOT interrupt the PHIL device injection for longer than three minutes prior to re-establishing injection. This may cause solidification of the PHIL device within the microcatheter tip resulting in microcatheter occlusion. Use of excessive pressure to clear the microcatheter may result in microcatheter or vessel rupture and embolization of non-target areas.
- The PHIL Liquid Embolic System is provided sterile and non-pyrogenic unless the unit package is opened or damaged. Do not use if the packaging damaged. Use before expiration date noted on the product packaging.
- The PHIL Liquid Embolic System is intended for single use only. The kit is intended to be used for one patient. Do not resterilize and/or reuse the device. Reuse and/or resterilization can increase risk of injection, cause a pyrogenic response or other life-threatening complications.
- Caution is to be used for nickel-sensitive and/or pregnant female patients, as the device packaged in glass syringes may contain Nickel.

Cautions

- Do not use if packaging is opened or damaged.
- This device is intended for single use only. Do not reuse, reprocess, or re-sterilize. Reuse, reprocessing, or re-sterilization may compromise the integrity of the device and /or lead to device failure which, in turn, may result in patient injury, illness, or death. Reuse, reprocessing, or re-sterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including but not limited to, the transmission of

infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

- After use, dispose in accordance with hospital, administrative and/or local government policy.

Precautions

- The safety and effectiveness have not been studied in the following patient populations:
  - Pregnant and nursing women
  - Individuals less than 18 years old
  - Individuals with feeding pedicle aneurysms not associated with the nidus, or distal feeders to the nidus or vascular malformation.
- Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.
- A garlic-like taste may be noted by the patient with use of the PHIL device due to the DMSO component. This taste may last several hours. An odor on the breath and skin may be present.
- Inspect product packaging prior to use. Do not use if sterile barrier is open or damaged.
- Use prior to expiration date.
- Verify that the microcatheters and accessories (see directions for use) used in direct contact with the PHIL polymer are clean and compatible with the material and do not trigger polymerization or degrade with contact. Use only DMSO compatible microcatheters indicated for use in the neuro or peripheral vasculature, and MicroVention sterile, prefilled syringes. Other microcatheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to microcatheter degradation. Refer to the Warnings and Directions for Use sections.
- Upon completion of the PHIL device injection, wait three minutes, slightly aspirate the syringe, and then gently pull the microcatheter to separate it from the PHIL cast. Failure to wait this recommended time to retrieve the microcatheter after injection may result in fragmentation of the PHIL device into non-target vessels.

1.4.3 Potential Complications / Adverse Effects

The potential complications / adverse effects for the PHIL device include, but are not limited to:

- Hematoma at the puncture site
- Non-target arterial thrombosis
- Ischemic events due to embolic migration, vasospasm, thrombosis
- Hemorrhagic accidents: vascular rupture – perforation

- Hemodynamic changes induced by the embolization may result in hemorrhagic complications
- These ischemic or hemorrhagic complications may result in various functional neurological deficits, stroke, and possibly death.

Users and/or patients should report any serious incidents to the manufacturer and the Competent Authority of the Member State or Local Health Authority in which the user and/or patient is established.

1.4.4 Other Aspects of Safety

Data relevant to the clinical safety and performance of the PHIL devices was collected and evaluated from routine data sources from PMS such as complaints, Corrective and Preventative Action (CAPA) and Field Action (01 Mar 2021 to 28 Feb 2025), as well as post-market clinical follow-up (PMCF).

The data has demonstrated the clinical safety of the subject devices:

- There were 23,601 units shipped between 01 March 2021 to 28 February 2025, and there were 30 complaint records, for an overall complaint rate of 0.13%.
- There were 4 MDV events associated with the subject device during the PMS review period, including EU, for a reportable complaint rate of 0.0169%.
- During the current review period, there was one Field Action (FCA2021-01) opened for PHIL for the evaluated period, which was initiated on February 2021 and closure report was submitted on June 2022.
- During the current review period, ten (10) CAPAs opened or in process that pertained to PHIL. Eight (8) of these CAPAs have been closed, and one (1) is in investigation stage and (1) is in effectiveness check stage.

The clinical evidence generated through this PMS will be used in the clinical evaluation of PHIL devices, with the aim of confirming the safety and performance throughout the expected lifetime of the device, of ensuring the continued acceptability of identified risks and of detecting emerging risks.

1.5 Summary of the Clinical Evaluation and PMCF

A Clinical Evaluation of the PHIL liquid embolic system is continuously updated and conducted in accordance with the requirements in MEDDEV.2.7.1 Revision 4 – Guidelines on Medical Devices – Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies. It includes the following:

- Literature Based Safety Appraisal
- A search of published relevant and available scientific literature was performed to assess the risks and benefits associated with other competitive predicate devices.

- Summary of Clinical Studies
- MicroVention has gathered data from post-market Trials/ Studies/ Registries under its sponsorship in which PHIL liquid embolic system were utilized
- Performance and Safety - Design Verification and Validation Data Analysis
- Product Literature and Instructions for Use
- The CER includes the methodology, literature references and conclusions and are reviewed and signed by an appropriately qualified physician.

The Clinical Evaluation Report, documents available clinical data relevant to the PHIL liquid embolic system. The available clinical data was collected, appraised, and analyzed, and it was determined that there is sufficient clinical evidence on the safety and performance in accordance with the intended purpose.

The Clinical Evaluation Report documents the benefit-risk profile, including side-effects, in the intended target patient populations and medical indications by assessing the clinical evidence against the hazards and patient harms as informed by the Risk Management and Post-Market Surveillance (PMS) documentation. The report also demonstrates the acceptability of the benefit-risk profile based on the current knowledge and state of the art in the concerned medical fields. Therefore, the clinical evaluation has established that the available clinical data are sufficient to establish conformity with all relevant Safety and Performance Requirements (Annex I) of EU MDR 2017/745 and confirm the safety and performance of the PHIL liquid embolic system.

In addition, Post-Market Surveillance (PMS) is a continuous process at MicroVention to gather, record, and analyze relevant data on the quality, performance and safety of a device throughout its entire lifetime actively and systematically. The planning and execution of PMS are conducted in accordance with the European Medical Device Regulation (MDR (EU) 2017/745), Chapter VII, Section 1 Post-Market Surveillance and MicroVention Post Market Procedures.

Given the evidence and data presented in the clinical evaluation and post market surveillance, and when the PHIL liquid embolic system is used according to the manufacturer's Instructions for Use, the risk to benefit profile is deemed acceptable.

1.5.1 Equivalent Device Clinical Data

Equivalency is not claimed in the clinical evaluation for the PHIL liquid embolic system.

1.5.2 Pre-CE-Mark Clinical Data

There were no EU pre-market clinical studies conducted for the PHIL Liquid Embolic System devices.

1.5.3 Clinical Data

Clinical data sources to evaluate the safety and performance of the PHIL Liquid Embolic System was collected from the following reputable data sources:

- **Post-Market Clinical Studies**
  - PHIL in the Treatment of Intracranial dAVF (NCT03467542) – completed, but pending clinical data to be published
  - PHIL Evaluation in the Endovascular Treatment of Intracranial Dural AVF (NCT03317821) – completed/published (summary of the data is included in published literature section of CER22-0004) (Ref ID 23)
  - PHIL fluid embolic system in dAVF embolization: PHIL Japan Study (NCT N/A) – completed, but pending clinical data to be published
  - PHIL Embolic System Pediatric IDE (Study of PHIL Embolic System in the Treatment of Intracranial Dural Arteriovenous Fistulas in the Pediatric Population (NCT03731000) – study is recruiting
  - PHIL Evaluation in the Endovascular Treatment of Intracranial Cerebral AVM – terminated in July 2021 due to low enrollment
- **Published Peer-reviewed Clinical Literature**

  The literature search detailed in this report presents relevant clinical data from the scientific literature for the PHIL™ Embolic System, conducted with sound methodological quality, scientific validity, and relevance to the device's fields of use. The review identified 25 publications totaling 763 patients treated with PHIL across neurovascular and peripheral indications. Neurovascular lesions included brain AVMs and dAVFs (e.g., Ref #2, 3, 16, 23, 41, 55, 57, 59, 72, 87, 99, 107, 190, 339); peripheral/visceral applications covered non-neurological bleeding, peripheral AVMs/AVFs, endoleaks, and hypervascular tumors (e.g., Ref #12, 45, 51, 52); and the dataset also includes chronic subdural hematoma (cSDH) (Ref #60, 309, 339). Of the 25 included references, seven publications are case reports (Ref #6, 7, 25, 56, 99, 111, 339).

  Across the 25 publications, PHIL demonstrated high technical success (87.5%–100%), immediate angiographic occlusion of 52%–100% and follow-up occlusion of 33.3%–100%, with follow-up windows typically 45 days to 12 months (isolated reports extend longer). Functional outcomes were favorable—mRS 0–2 at follow-up generally 87.5%–97.9% and symptom/clinical improvements were frequently reported. Peri and postprocedural adverse events reflected known endovascular risks (hemorrhagic and ischemic events, catheter/device issues), and several cohorts reported no complications; where explicitly assessed, recurrence was low (e.g., 2.1%) within stated windows. Collectively, the 25-publication evidence base, spanning AVM/dAVF, peripheral/visceral vascular lesions, cSDH (Ref #60, 309, 339), and seven case report–type publications (Ref #6, 7, 25, 56, 99, 111, 339) supports a favorable safety and performance profile for PHIL across the covered indications and timeframes. There were no systematic misuses or off-label uses of the subject device identified in this report.

- Relevant data collected from PMCF activities in the PMCF Report described as routine data sources were integrated into the above data sections. These data sources include,
  - Scientific Literature
  - Registries
  - Sponsor-initiated post-market clinical studies
  - Investigator-initiated post-market clinical studies
  - There were no additional PMCF activities initiated to address specific findings of the previous clinical evaluation.

1.5.4 Clinical Performance and Safety

Adverse events reported in the published literature associated with the use of the PHIL device included vessel/tissue damage (perforation 2.8%, dissection 0%) and hemorrhage (ICH 3.7%, SAH 5.6%–9.1%), as well as thrombo-embolic/ischemic events (11.1%). Additional device/access-related events observed included microcatheter retention (0%–9.1%) and embolic migration/fragmentation (2.8%–3.9%). All-cause mortality across heterogeneous cohorts ranged 0%–40% within reported follow-up windows (~45 days to 12 months), with multiple cohorts reporting 0% mortality and no complications. Overall, treatment using the PHIL™ device has been associated with an acceptable level of procedural safety within the reported horizons; observed morbidity (3.9%–4.3%) and event patterns align with the known risks of intracranial/peripheral endovascular embolization procedures. The Upper-bound mortality (40%) is driven by a very small series (n=5) at 3-month follow-up; it is not representative of larger datasets.

The AEs associated with the use of the PHIL Embolic System reported in the published literature were generally categorized in correspondence with the risks identified during the risk assessment process. There were no new risks identified in the published literature that were not already considered through the risk management process.

The clinical benefits of the PHIL Embolic System in embolization of peripheral and neurovascular lesions including bAVM, dAVF, peripheral AVM, various peripheral vascular lesions, as well as hypervascular tumors have been demonstrated by favorable angiographic and clinical outcomes, including technical success (complete occlusion/obliteration of nidus or successful PHIL embolization) achieved in 87.5%-100% of the patients, immediate occlusion of 52-100%, complete occlusion rate of 33.3%-100% (at ~45 days to 12 months follow-up), and good clinical outcome (mRS 0-2 at follow-up) of 87.5%-97.9% at follow-up (~45 days-12 months).

The clinical benefits are measured with technical success of the PHIL embolic agent implantation, immediate angiographic vascular lesion occlusion, as well as follow up angiographic occlusion and clinical outcomes evaluated with improvement of clinical symptoms, AVM/AVF downgrading, recanalization / recurrence, or neurological function mRS scores (0-2). The clinical literature data reported that the PHIL Embolic System use was associated with high rates of technical success, immediate angiographic occlusion or nidus obliteration, favorable follow up

angiographic occlusion, and zero recurrence. These results are in line with the results generated from alternative treatments or the state of the art.

Overall, treatment using the PHIL Embolic System has been associated with a high level of procedural safety and effectiveness, which has been consistently observed in all existing prospective trials and published literature. The good angiographic and clinical outcomes (indicated with complete angiographic occlusion of the embolized vascular lesion, or complete nidus obliteration of the embolized AVM, or favorable mRS 0-2) as well as the morbidity and mortality reported in most published data associated with the use of the PHIL Embolic System were in line with the rates associated with similar liquid embolic agents.

1.5.5 Post-Market Clinical Follow-up

From the evidence provided in this clinical evaluation, no PMCF studies are required for the PHIL Liquid Embolic System. The level of clinical evidence presented in this report is sufficient to support conformity to the relevant Essential Requirements, including a favorable benefit/risk ratio. No potential residual risks and/or unclarity on long term clinical performance that may impact the benefit/risk ratio were identified. No concerns were identified regarding the benefit-risk determination, the consistency of that evidence with the intended purpose, including the medical indication(s). This clinical evaluation has demonstrated that the PHIL Liquid Embolic System maintains an acceptable safety and performance profile and did not identify any questions relating to clinical safety or performance (i.e., residual risks) when used in accordance with its approved labelling.

1.6 Possible Diagnostic or Therapeutic Alternatives

1.6.1 Treatment Options and Interventions

Endovascular embolization is a minimally invasive procedure that blocks blood vessels supplying a tumor or abnormal vessels. It is done while preserving normal blood flow in the surrounding regions to maintain tissue health while concurrently dealing with problematic bleeding.

Treatment with an embolization procedure results in the deliberate obstruction of a blood vessel for a medical benefit. Catheter-directed embolization of peripheral and neurovascular AVMs and other lesions, including AVFs and hypervascular tumors, has been shown to result in major clinical improvement or complete disappearance of symptoms in the vast majority of patients. During these procedures, the blood vessel of interest is obstructed with an embolic agent. The type of agent utilized depends on a number of factors, including the type and size of blood vessel, and the need for a temporary or permanent blockage of the blood vessel. Embolic materials include:

- Particulates
- Mechanical
- Liquids/Gels

Particulates

Particulates are the most commonly used embolic agent due to the variety of available sizes, shapes, and properties (permanent, biodegradable, natural, synthetic, etc.), with microspheres often preferred due to their controllable shape and size distribution (Hu et al., 2019, Santoro et al., 2019). Particulates are delivered proximally to the target vasculature via a catheter. The particles are then driven, via blood flow, into the smallest space they can fit. Once lodged within the vessel, they mechanically obstruct flow and thrombus formation begins. Particulates are typically used when the target vasculature for thrombosis formation are small vessels including capillaries. Drawbacks include unintentional occlusion of larger proximal vessels due to clumping of particles and downstream embolization due to size and shape irregularity.

Mechanical

Mechanical embolization devices include coils and vascular plugs that allow complete occlusion of a specific vascular site. These devices are used in vessels of various sizes, including large vessels (Hu et al., 2019, Santoro et al., 2019). Coils and plugs are typically permeant implants with bioinert metallic cores (e.g., stainless steel, platinum, nitinol). During the procedure, the implant is placed in the desired location via a catheter. Once positioned, the implant expands into its preformed geometry in the vessel lumen. The expansion of the device creates radial force for vessel wall apposition, anchoring the device in place. The embolization of the vessel is achieved, in the use of coils by filling the space within the anchoring coil with additional coils, if needed. An occlusive membrane supported by the braided wire mesh core results in embolization when plugs are used. The positioning of the coils or plug is then confirmed by radiography. Both coils and plugs are also used in conjunction in some cases (Adachi et al., 2020, Jardinet et al., 2020).
Mechanical embolization devices are used to treat pulmonary and peripheral AVMs (Adachi et al., 2020, Bailey et al., 2019, Greene and Burrows, 2020, Gupta et al., 2020, Hawkins and Chewning, 2019), as well as a number of other issues.

Liquids/Gel

Liquid/gel embolic agents used in peripheral interventions have the ability to penetrate into smaller or more complex vascular targets where catheters and larger embolic therapeutics cannot (Hu et al., 2019, Santoro et al., 2019). This type of embolic agent blocks blood flow by chemically forming a permanent cast and does not depend on the patient's coagulation system for thrombosis formation. One type of liquid/gel embolics are sclerosing agents, ethanol being the most common, which functions by denaturing vessel endothelium and causing necrosis of vascular structures, such as AVMs (Kim et al., 2020, Bouwman et al., 2020). Other forms of liquid/gel embolic include in-situ polymerization (TRUFILL) which is commonly known as "glue" and *in-situ* precipitating fluids (Onyx, PHIL) which create casts when exposed to body fluids in the target vasculature. Drawbacks of liquid/gel embolics include cardiopulmonary complications (ethanol), necrosis of non-target tissue, nerve injury, distal thrombolysis, as well as with agents such as Onyx, high cost, radiopacity and residual mass effect (Bouwman et al., 2020, Kim et al., 2021).

Unlike other liquid embolics, the PHIL system radiopacifier is an integral part of the co-polymer (homogenous radiopacification); the inclusion of a nonmetallic radiopaque agent results in fewer artifacts with CT or magnetic resonance imaging (MRI) imaging.

Interventions for AVMs and Hypervascular Tumors

Treatment for AVMs and hypervascular tumors depends on a number of factors. Treatment goals may include during the lesion via embolization or reducing blood flow to make surgical removal saver. Current treatment options include the microsurgical removal of the AVM, or radiation therapy, which uses X-rays and other high-energy rays to destroy the cells at the AVM. In addition, both AVMs (and AVFs) and hypervascular tumors can be treated via embolization. Embolization blocks the blood flow in the vessels targeted, leading to a reduction in the AVM or ABF or reducing or stopping blood flow to the tumor (Pierot et al., 2013, Triano et al., 2020, Vollherbst et al., 2022).

Liquid embolic agents are used to induce occlusions in a region of a blood vessel of interest. These agents polymerize after contact with blood to form a solid material. The PHIL liquid embolic system is intended for use in the embolization of lesions in the peripheral and neurovasculature. Liquid embolics are utilized when other treatments, such as medications and life-style changes, are no longer a viable option (Lucatelli et al., 2021, Vollherbst et al., 2022).

Arteriovenous Malformations

Treatment for AVMs depends on where the abnormality is found, the patient's signs and symptoms and overall health, and the risk of treatment. Sometimes, an AVM is monitored with regular imaging tests to watch for changes or problems. Other AVMs require treatment. Determining whether an AVM needs treatment involves factors including whether the AVM:

- Bleeding history
- Is causing symptoms other than bleeding
- Is in a part of the brain where treatment can be safely provided

The main treatment for AVM is surgery. The surgery might completely remove the AVM. This treatment is usually used when the AVM is in an area where surgeons can safely and easily remove the AVM, with little risk of causing significant damage to the brain tissues. As mentioned above, endovascular embolization, such as with a liquid embolic agent, is a type of surgery that is also utilized to treat AVMs (Giurazza et al., 2021). Stereotactic radiosurgery using highly focused beams of radiation to damage the blood vessels and stop the blood supply to the AVM, may also be used to treat AVMs (Chen et al., 2020).

Hypervascular Tumors

A hypervascular tumor is a tumor that has an abnormally large number of blood vessels attached. The elevated number of blood vessels may increase the risk of bleeding, and for this reason hypervascular tumors can often be difficult to remove. Reducing or eliminating this excessive blood flow feeding the tumor aids in the treatment. Liquid embolic agents are effectively utilized

to treat these tumors, reducing or stopping the excessive blood flow to the tumor by blocking the vessels targeted (Pedicelli et al., 2020).

1.6.2 Available Technologies

Liquid embolic systems such as those listed within the PHIL liquid embolic system, are well established medical devices with numerous types and styles available from a variety of manufacturers. An example of the liquid embolic system similar to the PHIL liquid embolic system is provided in table below.

Table 1.4: Similar Devices

Similar Device	Manufacturer	Intended use
Onyx® LES	Medtronic	The Onyx® LES is used for presurgical embolization of brain arteriovenous malformations (bAVMs).

1.7 Suggested Profile and Training for Users

The PHIL Liquid Embolic System should be used only by physicians with neuro or peripheral interventional training and a thorough knowledge of the vascular pathology to be treated, vascular architecture, angiographic techniques, and super-selective embolization techniques.

1.8 Reference to any Harmonized Standards and CS

Standard Number	Edition	Standard Title (equivalent edition)
EN ISO 13485	2016/A11:2021	Medical devices - Quality management systems - Requirements for regulatory purposes (ISO 13485:2016)
EN ISO 14971	2019/A11:2021	Medical devices - Application of risk management to medical devices (ISO 14971:2019)
EN IEC 60812	2018	Failure modes and effects analysis (FMEA and FMECA) (IEC 60812:2018)
EN 62366-1	2015/A1:2020	Medical devices - Part 1: Application of usability engineering to medical devices (IEC 62366-1:2015/A1:2020)
EN ISO 14155	2020	Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2020)
ISO/TR 20416	2020	Medical devices - Post-market surveillance for manufacturers
EN ISO 15223-1	2021	Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements (ISO 15223-1:2021)
EN ISO 20417	2021	Medical devices - Information to be supplied by the manufacturer (ISO 20417:2021, Corrected version 2021-12)
EN ISO 11607-1	2020/A1:2023	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2019/Amd 1:2023)
EN ISO 11607-2	2020/A1:2023	Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes (ISO 11607-2:2019/Amd 1:2023)
ISTA 3A	2018	Packaged-Products for Parcel Delivery System Shipment 70 kg (150 lbs) or Less
ASTM D4169	2023e1	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM D4332	2022	Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing

Standard Number	Edition	Standard Title (equivalent edition)
ASTM F88	2023	Standard Test Method for Seal Strength of Flexible Barrier Materials
ASTM F1886	2016	Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection
ASTM F1929	2023	Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration
ASTM F2096	2011R2019	Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)
ASTM F1980	2016	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
EN ISO 10993-1	2020	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2018, including corrected version 2018-10)
EN ISO 10993-3	2014	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity (ISO 10993-3:2014)
EN ISO 10993-4	2017	Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO 10993-4:2017)
EN ISO 10993-5	2009	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity (ISO 10993-5:2009)
EN ISO 10993-6	2016	Biological evaluation of medical devices - Part 6: Tests for local effects after implantation (ISO 10993-6:2016)
EN ISO 10993-10	2023	Biological evaluation of medical devices - Part 10: Tests for skin sensitization (ISO 10993-10:2021)
EN ISO 10993-11	2018	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO 10993-11:2017)
EN ISO 10993-12	2021	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (ISO 10993-12:2021)
EN ISO 10993-13	2010	Biological evaluation of medical devices - Part 13: Identification and quantification of degradation products from polymeric medical devices (ISO 10993-13:2010)
EN ISO 10993-17	2023	Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents (ISO 10993-17:2023)
EN ISO 10993-18	2020/A1:2023	Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process (ISO 10993-18:2020/Amd 1:2022)
EN ISO 10993-23	2021	Biological evaluation of medical devices - Part 23: Tests for irritation (ISO 10993-23:2021)
EN ISO 14644-1	2015	Cleanrooms and associated controlled environments - Part 1: Classification of air cleanliness by particle concentration (ISO 14644-1:2015)
EN ISO 14644-2	2015	Cleanrooms and associated controlled environments - Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration (ISO 14644-2:2015)
ANSI/AAMI ST72	2019	Bacterial endotoxins – Test methods, routine monitoring, and alternatives to batch testing
EN 556-1	2001/AC:2006	Sterilization of medical devices – Requirements for medical devices to be designated 'STERILE' – Part 1: Requirements for terminally sterilized medical devices
EN ISO 11737-1	2018/A1:2021	Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products (ISO 11737-1:2018/Amd 1:2021)

Standard Number	Edition	Standard Title (equivalent edition)
EN ISO 11737-2	2020	Sterilization of health care products - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process (ISO 11737-2:2019)
ISO 11737-3	2023	Sterilization of health care products - Microbiological methods - Part 3: Bacterial Endotoxin testing
EN ISO 11138-1	2017	Sterilization of health care products - Biological indicators - Part 1: General requirements (ISO 11138-1:2017)
EN ISO 17665-1	2006	Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 17665-1:2006)
EN ISO 10555-1	2013A1:2017	Intravascular catheters — Sterile and single-use catheters — Part 1: General requirements (ISO 10555-1:2013A1:2017)
EN ISO 80369-7	2021	Small-bore connectors for liquids and gases in healthcare applications - Part 7: Connectors for intravascular or hypodermic applications (ISO 80369-7:2021)
EN ISO 80369-20	2015	Small-bore connectors for liquids and gases in healthcare applications - Part 20: Common test methods (ISO 80369-20:2015)
EN ISO 14630	2012	Non-active surgical implants - General requirements (ISO 14630:2012)
ASTM F640	2023	Standard test methods for determining radiopacity for medical use
ASTM F2052	2021	Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment
ASTM F2119	2007R2013	Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants
ASTM F2182	2019e2	Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging
ASTM F2213	2017	Standard test method for measurement of magnetically induced torque on passive implants in the magnetic resonance
ASTM F2503	2023e1	Standard practice for marketing medical devices and other items for safety in the magnetic resonance environment

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