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"Evaluating The Safety And Efficacy Of Developed Extra Long Introducer Sheaths In A Swine Model"

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Abstract
The study aimed to evaluate the safety and performance of the Extra Long Introducer Sheath in a clinically relevant swine model. Two female swine were used in the study, with all animals passing the initial physical examination. The Sheath was deployed in the pulmonary artery, supported by three extra-stiff guide wires for a clinically relevant duration. Additional procedures included testing the trackability of the sheath and the inflation and deflation of the balloon dilatation catheter and navigator transcatheter heart valve delivery system. Simulations involved sequential removal of guide wires to assess the sheath's performance. Angiographic imaging confirmed prominent visualization and patency of the sheath with no thrombus formation. Post-procedural necropsies revealed no thrombus or injury to the pulmonary artery, iliofemoral vein, or inferior vena cava. Hematological and clinical chemistry parameters showed no significant changes before and after the procedure. The Anticoagulated vessel implant scoring scheme rated the sheath as thromboresistant, with a mean score of 0, indicating no significant thrombosis. The study concluded that the Extra Long Introducer Sheath is safe, does not cause adverse effects on target regions, and effectively supports procedures like balloon catheter and valve delivery device navigation in the pulmonary artery. No adverse events or safety concerns were identified, confirming the sheath's suitability for clinical applications.

Keywords: *Extra Long Introducer Sheath, Swine Model, Safety Evaluation, Thromboresistance, Pulmonary Artery, Endovascular Devices, Vascular Access, Medical Device Evaluation*

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I. Introduction

The Extra Long Introducer Sheath is a medical device intended to be inserted into the vasculature to provide a conduit for the insertion of endovascular devices while minimizing blood loss. The purpose of this study was to evaluate the safety and performance of the Extra Long Introducer Sheath in a clinically relevant swine model as a single-arm evaluation of regional and downstream thromboresistance. The study was conducted in compliance with ISO 10993-4:2017(E) for the in vivo category of tests to evaluate thrombosis. A swine model was chosen because the anatomy and vascular response properties correlate well with humans, and it is a commonly used model for evaluating similar devices. The iliofemoral vein was dilated, and the 14Fr to 26Fr Extra Long Introducer Sheath was inserted via the femoral vein and tracked into the pulmonary artery. The sheath was dwelled for three times the longest expected clinical dwell time of two minutes. Activated Clotting Time (ACT) was measured to ensure clinically relevant anticoagulation levels were maintained.

Conventional length sheaths have some limitations, such as providing less support and stability during catheter advancement, which increases the risk of vascular trauma or damage to the vessel wall. Additionally, short introducer sheaths may offer less effective hemostasis (control of bleeding) compared to longer sheaths, particularly in cases where prolonged catheterization or multiple device exchanges are required. In contrast, aforementioned longer sheaths can be advantageous for certain advanced procedures that require facilitating complex maneuvers or accessing specific anatomical locations, which short introducer sheaths may not adequately support. Longer sheaths generally offer more effective hemostasis control due to their increased length, which helps reduce bleeding complications after procedures. The Extra Long Introducer Sheath is an excellent solution for delivering stents and valves in the right heart, including the right ventricular outflow tract (RVOT), main pulmonary artery (MPA), and its branches. Its innovative dilator tip design allows the sheath to be tracked over up to three guidewires of 0.035 inches in thickness, significantly enhancing trackability.

At the conclusion of the simulated use, the sheath was withdrawn and evaluated for thrombus formation. Radiographic images were taken to confirm placement and evaluate thrombogenicity. A comprehensive necropsy was performed to examine the implantation site and downstream vasculature for any

device-associated clot or abnormalities. The results of this study helped us to determine the safety and performance of the Extra Long Introducer Sheath for its intended use of providing vascular access while minimizing thrombotic complications.

II. Materials And Methods

Medication Details:

Details of the drugs used for pre-operative and post-operative in this study are given in following table:

Table 1: Details of medications used in the study

Drug name	Manufactured by	Batch / Lot No.	Expiry date
Ketamine	Troikaa pharmaceuticals Ltd	K50514	Sep 2023
Xylazine	IIL India	FHK1003	Jan 2024
Propofol	Celon Labs	PF121906BCY	Jul 2023
Isoflurane	Neon Lab	KPNP700013	Aug 2025
Thiopentone Sodium	Neon Lab	173274	Dec 2023
Heparin	Gland Pharma Ltd	101109	Jul 2023
Aspirin	USV Ltd	52001055	Nov 2021
Clopidogrel	Cipla Ltd	SN91823	Oct 2021
Tramadol	Maxon Biotech Ltd	NC20025B	Aug 2022
Atropine	Pentagon Labs Ltd	19GAS002	Sep 2022

Animal Preparation:

The experimental procedure began with the weighing of the study animal, followed by the administration of preanesthetic atropine at a dose of 0.05 mg/kg. Anesthesia induction was then initiated using 15 mg/kg of Ketamine administered intramuscularly (IM), along with 2.5 mg/kg of Xylazine IM, and 1-3% Isoflurane inhalation anesthesia through a face mask. Additionally, a Propofol bolus of 0.5 mg/kg was administered intravenously (IV) to facilitate induction. The specific volumes of each drug used in the experiment were meticulously recorded in the raw data. Prior to the introduction of the sheath and electrode placement for ECG monitoring, the animal's hair was clipped in the groin region. Once it was confirmed that there were no glottis reflexes present, the animals were intubated using an intratracheal tube of appropriate size. Throughout the duration of the experiment, animals were maintained under general Isoflurane anesthesia, with anesthesia levels ranging between 1-3%.

Individual Body Weight:

Table 2: Body weight

Animal Number	Sex	Treatment (Day 0)
P1	Female	54.2 kg
P2	Female	70.1 kg

Note: kg - Kilograms.

Diet and Water

The source of the water provided ad libitum is borewell water, which is purified using an RO water plant present on the premises. Swine grower feed was provided to the animals.

Test System

Justification for the Selection of Test System: A swine model was chosen due to its extensive use in evaluating the balloon dilatation catheter and Navigator transcatheter heart valve delivery system. This model has generated a substantial amount of data on vascular response properties, correlating well with human vascular responses, and meets most regulatory requirements. The swine model is commonly used to evaluate the safety and performance of the Extra Long Introducer Sheath, Heart Pulmonary Artery Valve, or Pulmonary Artery stent Delivery System, as it is a clinically relevant species. Swine and human veins have similar anatomy, and the swine model is recommended for preclinical studies by the FDA and Schwartz et al., 2008.

Rationale of Insertion Site and Dwelling Time of Test Item Insertion Site: The iliofemoral vein was serially dilated using 6, 8, 10, 12, 14, 16, 18, 20, and 22Fr dilators. The Fr 14Fr to 26Fr Extra Long Introducer Sheath, equipped with a 3-hole dilator, was then tracked over 3 wires into the branch Pulmonary Artery. It was inserted at the femoral vein above the inguinal ligament, maintaining an appropriate distance from the insertion site to its

proximal tip in the pulmonary artery. The Extra long Introducer Sheath and Navigator were each dwelled for 5 minutes in the pulmonary artery, with the insertion site and length being clinically relevant.

Dwell Rationale: The Long Sheath was dwelled for three times the longest expected clinical dwell time, which is over 2 minutes. A clinical simulation was performed with 3 guide wires; one guide wire was removed, and the Extra Long Introducer Sheath was dwelled on two guide wires. Subsequently, the second guide wire was removed, and the Long Sheath was dwelled on one guide wire.

Humane Care and Daily Observations: The study animals were monitored for health during their holding period and observed for any abnormalities.

Housing and Exercise: The animals were housed in cages that comply with the specifications outlined by CPCSEA. Each housing unit had a cage card indicating the unique identification number of the animal housed within. Cleaning of animal rooms, pens, and cages was performed according to SOP/PBS/ABH/061, with exercise managed by SOP/PBS/ABH/063.

Animal Welfare: The test facility was certified by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) for experimentation, with Certification No.: 1312/PO/RcBiBt-S/RcBiBt-L/09/CPCSEA

Device Description

Extra Long Introducer Sheath consists of an introducer tube with radiopaque distal tip and equipped with proximal haemostatic valve, two (2) Loaders and two extension lines with 3 way stopcocks. Extra Long Introducer Sheath is intended for insertion of THVR related hardware such as THV, Pulmonary stent, Guide wires, Balloon Dilatation Catheter, the THV pre-mounted on the balloon Transcatheter Heart Valve Delivery System in and out of patient's culature. The Extra Long Introducer Sheath is available in 14Fr to 26Fr size.

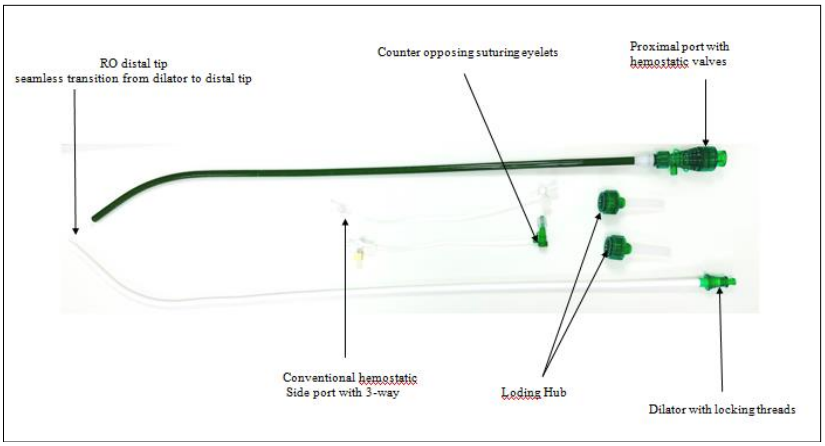

Figure 1: The Smart Extra Long Introducer Sheath

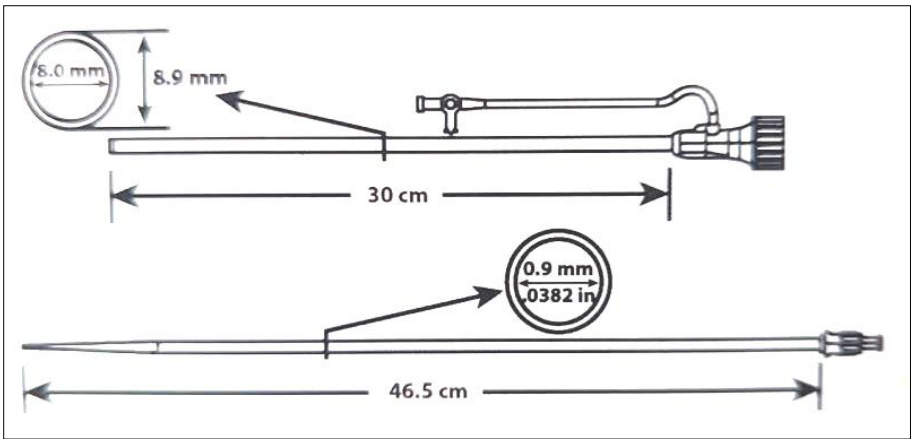

Figure 2: Schematic view of Conventional Introducer Sheath & Currently Developed Extra Long Introducer Sheath with Difference in Dimensions

Experimental Procedures

Fasting

Feed and water were withdrawn overnight prior to the procedure to prepare the swine for surgery.

Preparation of Test Item

The Extra Long Introducer Sheath was in its final sterile form and ready for use according to clinical procedure instructions.

Test Procedure

The primary goal was to evaluate the safety and performance of the Extra Long Introducer Sheath in a swine model, simulating pulmonary valvotomy and pulmonary artery stunting.

1. Dwelling Times for Test Items
- Iliofemoral Vein (Sheath): 20 minutes
- Pulmonary Artery in place): 5 minutes
- Pulmonary Artery (in place after removal): 5 minutes

2. Activated Clotting Time (ACT) Measurement
- Device: ACT II machine
- Blood Samples: Collected from the femoral vein sheath (approx. 2 ml per time point)
- Pre-heparin ACT: Approx. 89 seconds
- Heparin Administration: Maintained ACT between 250-350 seconds, occasionally reaching up to 355 seconds within the protocol limit of 500 seconds
- Frequency: ACT measured approximately every 20 minutes

Table 3: Activated Clotting Time (ACT) Measurement

Animal Number	Date	Time (min)	ACT Value
P1	01 June 2022	0	86
		60	245
		120	268
P2	01 June 2022	0	98
		60	290
		120	325

Note: Min-minutes; prior to test item insertion and un-heparinized blood sample

3. Animal Preparation and Procedure Details
- Anesthesia: Animals were anesthetized, and the introducer sheath was placed followed by heparinization.
- Angiographic Cine: Obtained to document patency and forward flow at the intended dwell zone.
- Insertion Technique: The Extra Long Introducer Sheath was inserted via the femoral vein using the Seldinger technique.
- Guide Wires: A diagnostic JR catheter and 260cm 0.035" Terumo guide wire were used to reach the pulmonary artery branches. The guide wire was exchanged with a super stiff guide wire, followed by insertion of additional guide wires.

4. Dilatation and Tracking
- Femoral Vein Dilation: Sequentially dilated using 12, 14, 16, 18, 20, and 22Fr dilators.
- Insertion of Sheath: The 14Fr to 26Fr Extra Long Introducer Sheath was tracked over three wires into the pulmonary artery branch.
- Trackability Assessment: The sheath's performance was evaluated over three, two, and one guide wire.

5. Hemostasis and Flushing
- Hemostatic Valve Check: Performed after removing the dilator and guide wire.
- Flushing: Sheaths were flushed with heparinized saline according to clinical techniques.
- Insertion of Devices: and systems were inserted through the Extra Long Introducer Sheath into the pulmonary artery.
- ACT Monitoring: Checked approximately every 20 minutes.

6. Radiographic Documentation
- Cine Images: Recorded to document the test item placement and dwell zones.

Post-Procedure Evaluations

- Thrombus Evaluation: At the end of the simulation, the Extra Long Introducer Sheath was withdrawn and evaluated for thrombus formation using light microscopy. No thrombus was observed, eliminating the need for SEM imaging.
- Terminal Heparinization: Followed by administration of thiopental sodium (100 mg/kg) to euthanize the animals.
- Necropsy: Comprehensive necropsy was conducted, including examination of the heart, whole body, all orifices, and thoracic and abdominal cavities. Photography documented the presence or absence of acute thrombosis.
- Procedure Repetition: The same procedure was repeated for both animals in the study.

Test Item Images: P1

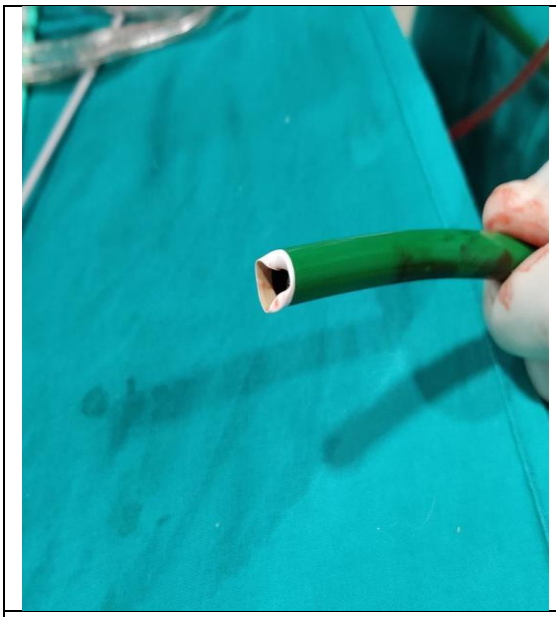

Figure 3: Image of the proximal end of Sheath (No thrombus)

Figure 4: Image of the proximal end of Sheath (No thrombus)

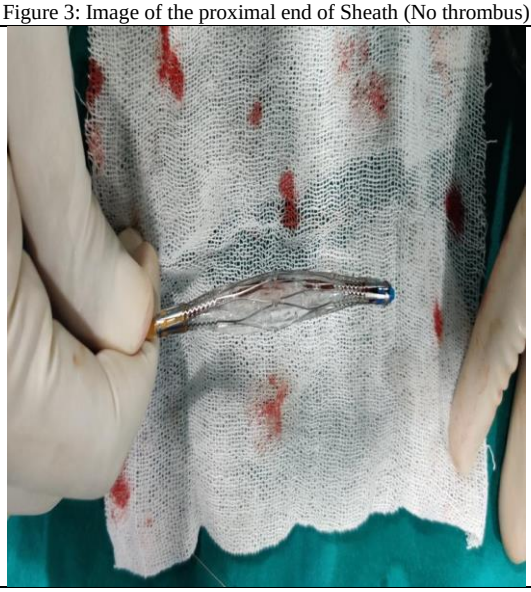

Figure 5: Image of balloon

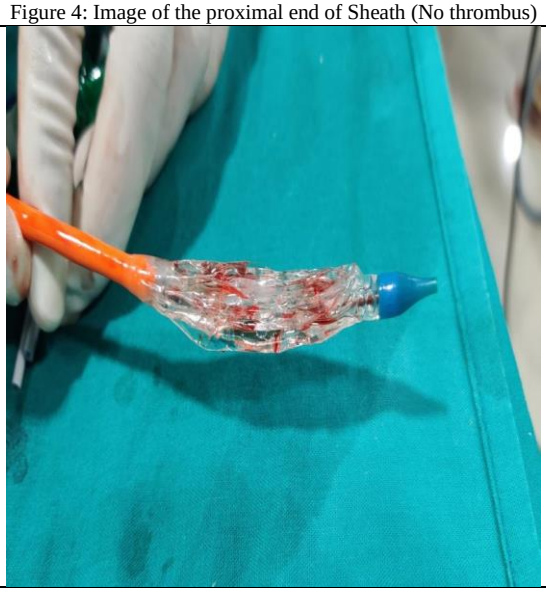

Figure 6: Image of Navigator

Test Item Images: P2

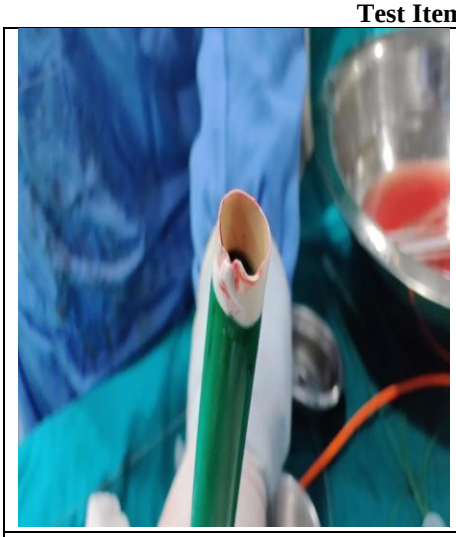

Figure 7: At the proximal end of the sheath, there is no evidence of thrombus observed.

Figure 8: In the image depicting the proximal end of the sheath, no thrombus was identified.

Figure 9: Necropsy image of the proximal end of the sheath IVC revealed a kinked.

Figure 10: The image depicts sheath's distal end with no evidence of leaking around the haemostat.

III. Pathology

Euthanasia

Immediately after completing the procedure, the animals were humanely euthanized with an injection of thiopentone (100 mg/kg) administered in the marginal ear vein.

Necropsy

A thorough gross necropsy and photography were conducted for the organs involved in the test item implantation and downstream organs to evaluate the local effects of thrombus formation. Initially, photographs were taken of the Extra Long Introducer Sheath in situ, followed by images of the explanted device to examine and document any vascular device-associated clots and downstream vascular findings. Similar assessments were conducted on explants from the left and right pulmonary arteries.

Thrombus formation was scored using the Anticoagulated Vessel Implant-score, in accordance with the scoring schema A of ISO 10993-4:2017, as follows:

Table 4: Thrombus Formation Score Description

Thrombus Formation Score Description	Score
No significant thrombosis (a very small clot was acceptable at insertion)	0
Minimal thrombosis, one location	1
Minimal thrombosis, multiple locations	2
Significant thrombosis, >1/4 to <1/2 the surface of the implant, vessel patent	3
Significant thrombosis, >1/2 the surface of the implant, vessel patent	4

Thrombus Formation Score Description	Score
Vessel completely occluded	5

The organs underwent a full gross evaluation with a focus on evidence of thromboembolism or other abnormalities. Both normal and abnormal findings were documented in writing and with digital photography. Observations for any abnormalities were examined in the tissues. Images were taken of the heart, kidneys, lungs and semi-membranous and semi-tendinosus muscles.

This summary provides a detailed yet concise account of the necropsy procedures, making it suitable for inclusion in an article.

Necropsy Image: P1 and P2

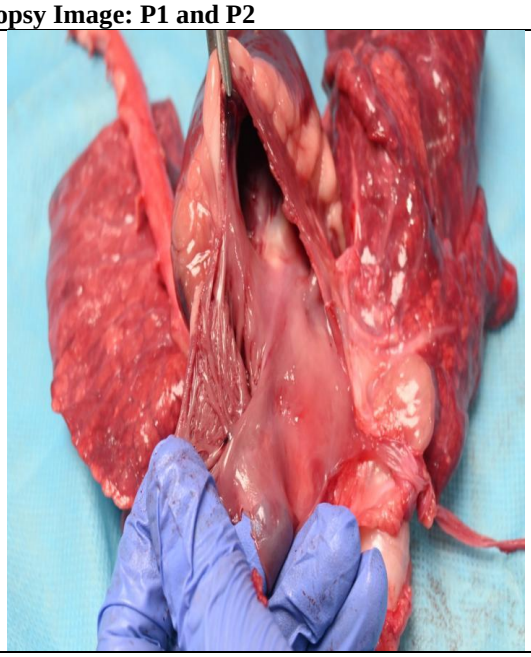

Figure 11: Images of Pulmonary artery sinus

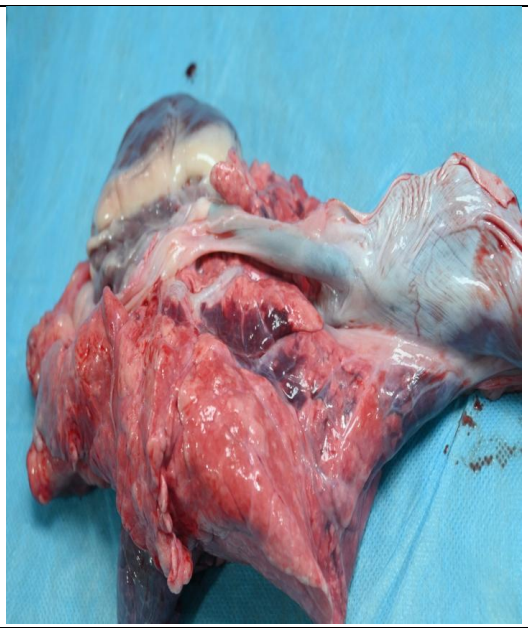

Figure 12: Images of Lung and Pulmonary artery

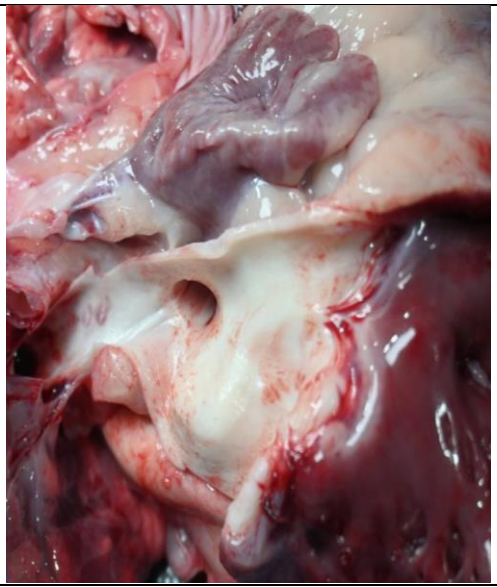

Figure 13: Images of lungs and

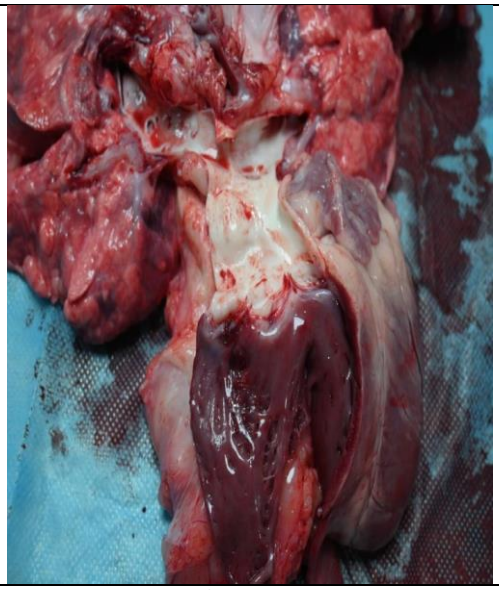

Figure 14: Images of semi-membranous and semi-tendeneaus sections

Angiography Images: P1

The Extra Long Introducer Sheath was inserted in the Pulmonary artery towards external iliofemoral vein having its proximal tip in the inferior vena cava and dwelled there.

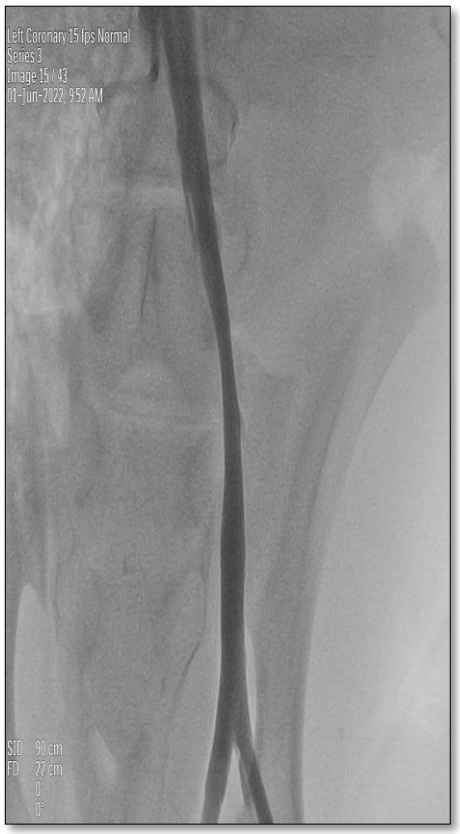

Figure 15: Baseline Angiography of Left Iliofemoral Vein.

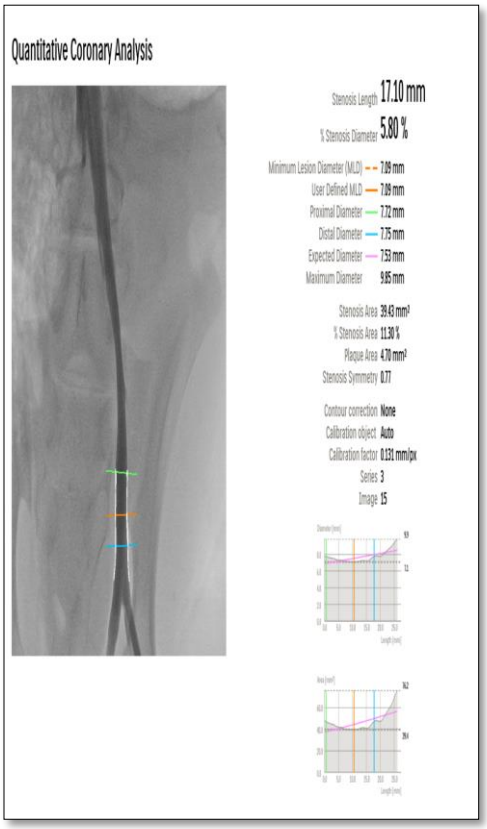

Figure 16: Left Iliofemoral Vein QVA.

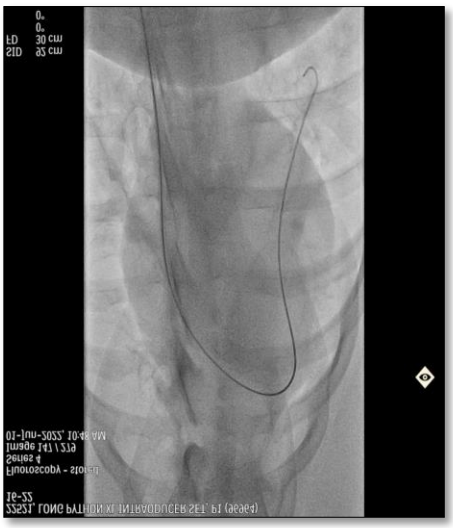

Figure 17: First guide wire placed in left pulmonary artery.

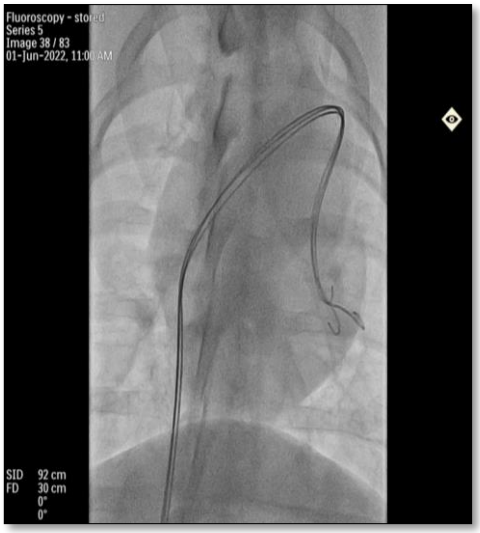

Figure 18: Three guide wires placed in left pulmonary artery from iliofemoral vein.

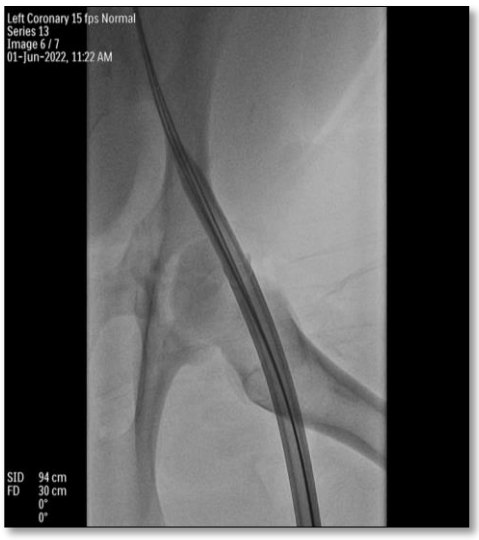

Figure 19: After dilating the iliofemoral vein, the guide wire was inserted, and the sheath was then advanced over it.

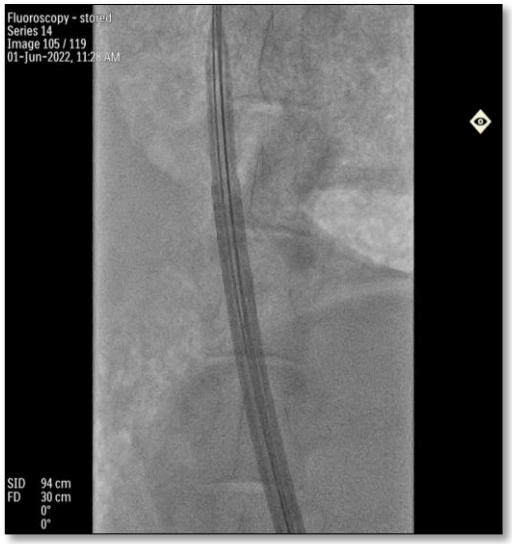

Figure 20: Extra Long Introducer Sheath was dwelling on three guide wires to support (Location-Inferior Vena cava).

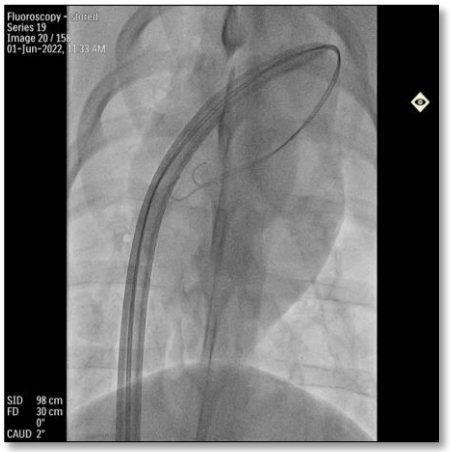

Figure 21: guide wires were exchanged from the left pulmonary artery to the right pulmonary artery, with an extra-long introducer sheath dwelling on two guide wires in the right pulmonary artery.

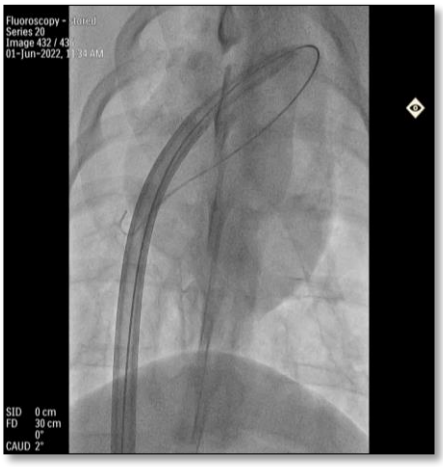

Figure 22: The Extra Long Introducer Sheath was inserted into the right pulmonary artery with one guide wire.

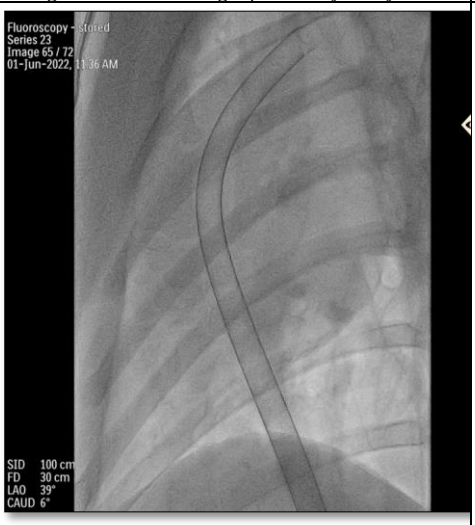

Figure 23: The dilator was removed, and the extra-long sheath was properly inserted into the right pulmonary artery.

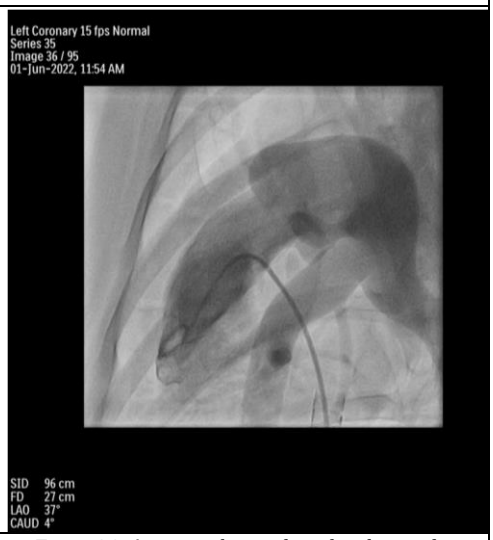

Figure 24: Angiography conducted with pigtail catheter support revealed no injuries in the pulmonary artery.

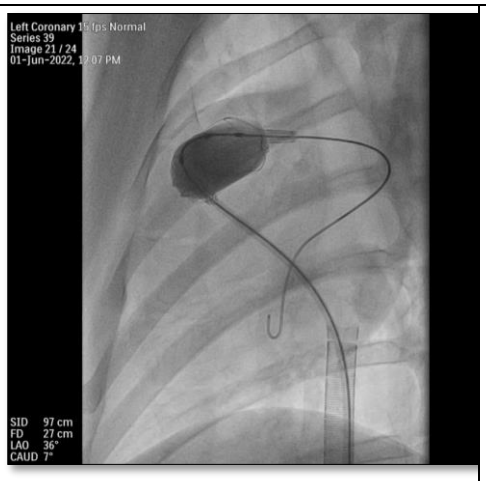

Figure 25: balloon checked into the Extra Long Sheath at pulmonary valve.

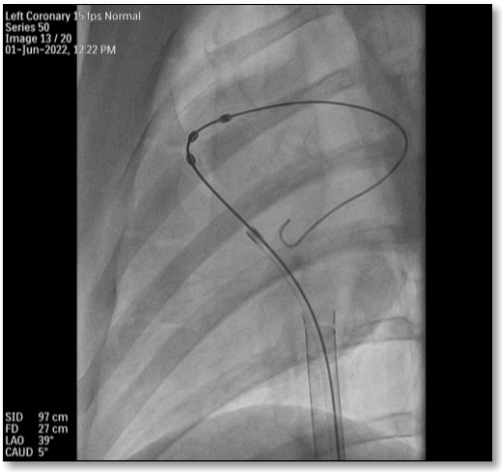

Figure 26: Navigator checked into the Extra Long Sheath at pulmonary valve.

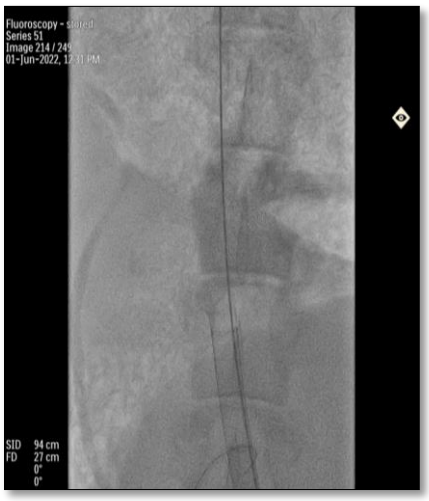

Figure 27: The Extra Long Sheath is being removed.

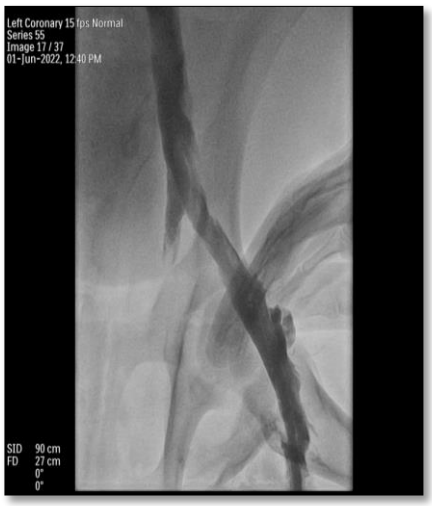

Figure 28: Following the removal of the Extra Long Sheath post-procedure, an angiogram was performed to assess the iliofemoral vein, revealing no observed injuries.

P2

Extra Long Introducer Sheath was inserted in the Pulmonary artery towards external iliofemoral vein having its proximal tip in the inferior vena cava and dwelled there.

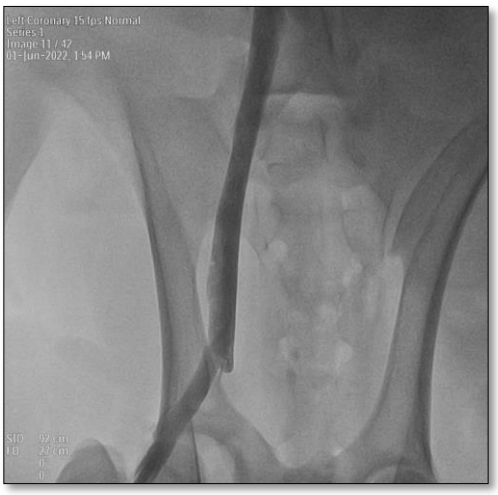

Figure 29: Baseline Angiography of Right Iliofemoral Vein.

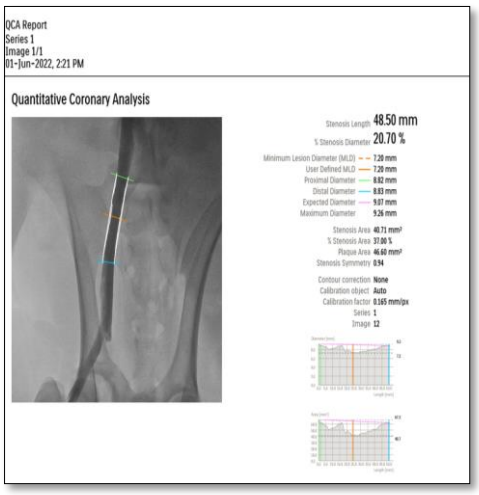

Figure 30: Right Iliofemoral Vein QVA.

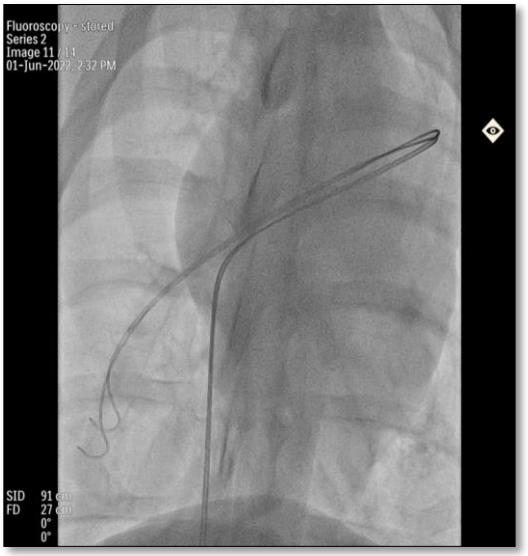

Figure 31: Two guide wires placed in right pulmonary artery.

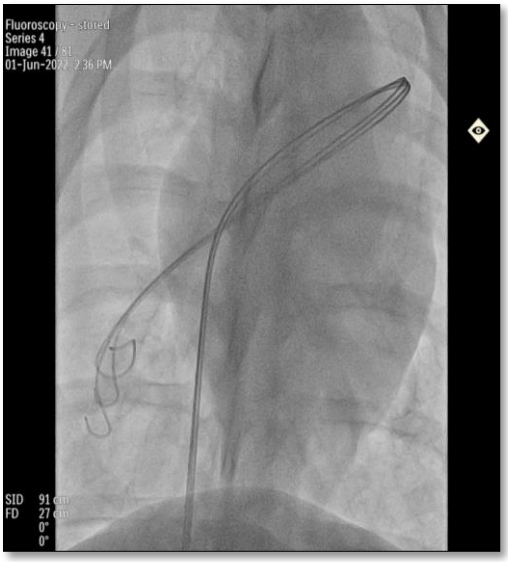

Figure 32: Three guide wires placed in right pulmonary artery.

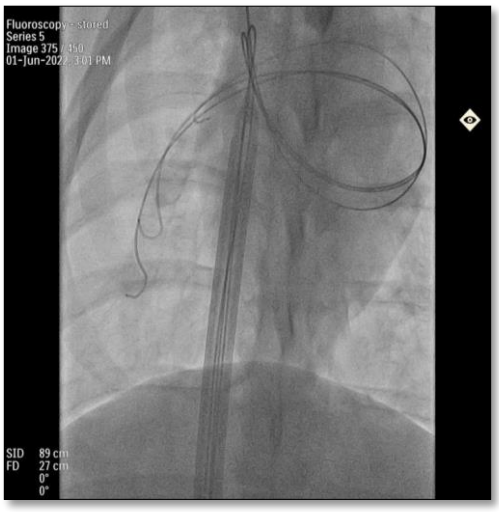

Figure 33: An acute angulation was noted in the right pulmonary artery, preventing the Extra Long Introducer Sheath from traversing the pulmonary artery branch.

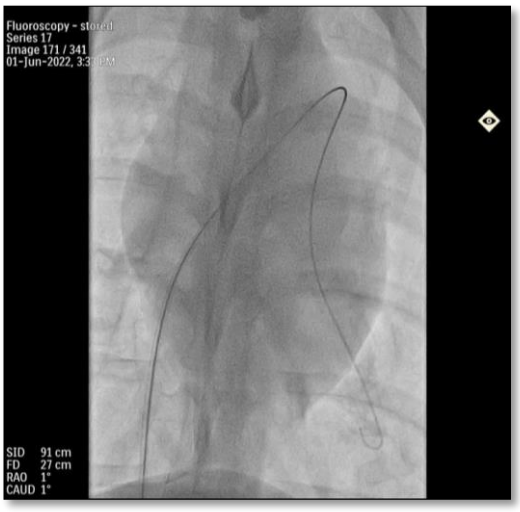

Figure 34: The first guide wire was replaced from the right pulmonary artery to the left pulmonary artery.

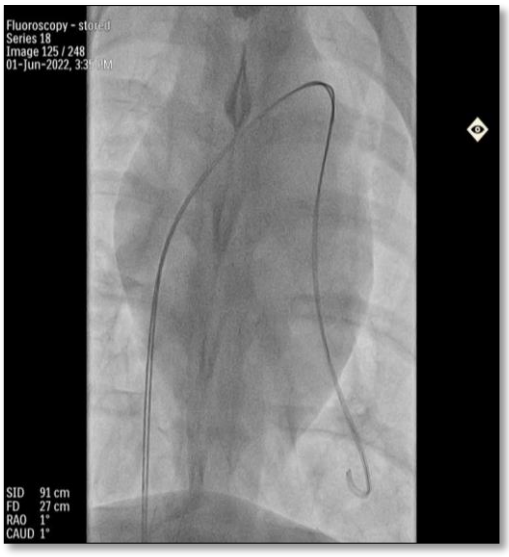

Figure 35: Two second guide wires were replaced from the left pulmonary artery.

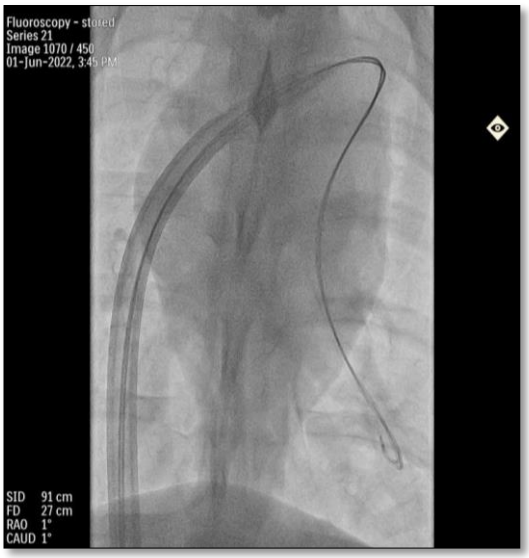

Figure 36: Extra Long Introducer Sheath was dwelling on two guide wires in Left Pulmonary artery.

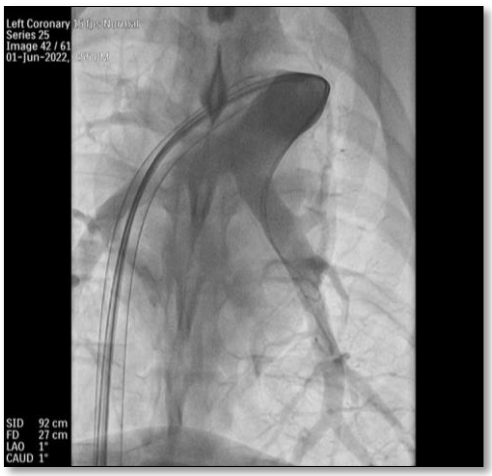

Figure 37: An angiographic examination was conducted with guide catheter support, revealing no observed injuries in the pulmonary artery.

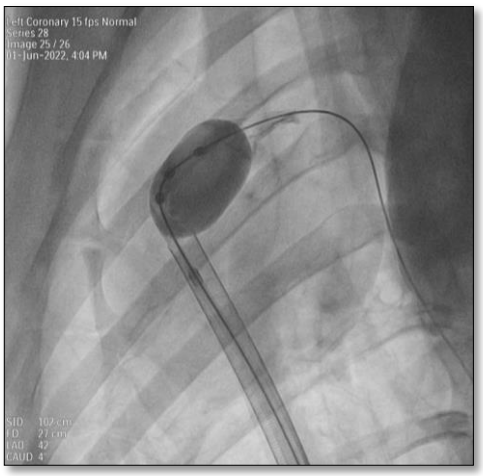

Figure 38: Navigator was checked into the Extra Long Sheath at pulmonary valve.

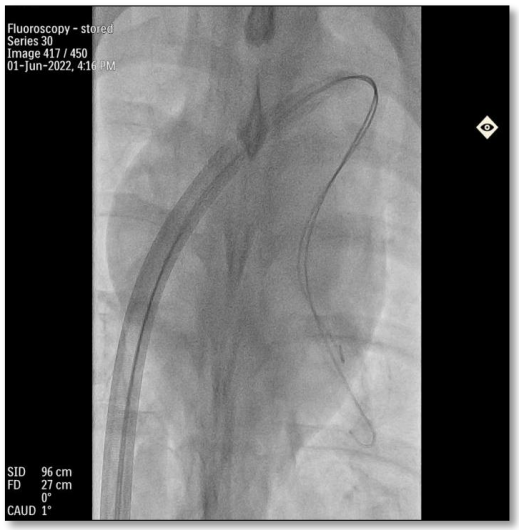

Figure 39: Extra Long Introducer Sheath was dwelling on two guide wire into the Left Pulmonary artery.

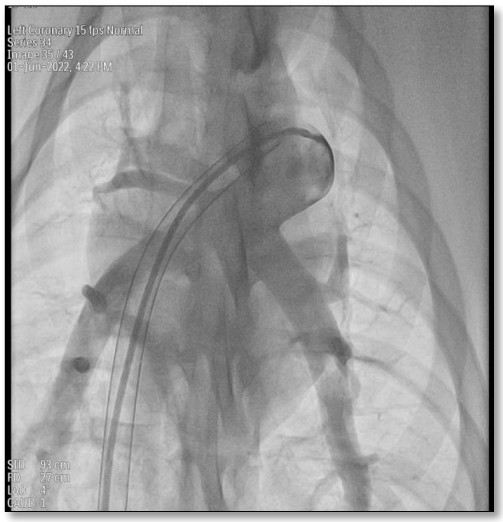

Figure 40: Following the procedure, a post-check angiogram was conducted with JR guide catheter support, revealing no observed injuries in the pulmonary artery.

IV. Results

Radiographic Thrombogenicity Evaluation

- Radiographic thrombogenicity evaluation images are depicted.

Morbidity/Viability

- There was no morbidity or early electives (death before completion of experiment).

Table No 5: Mortality

Animal Number		**96964, 96966**	**P1 & P2**
Sex		**Female**	**Female**
Day of Observations	Mortality	Incidences	Incidences
Acclimatization Phase (Day 1-7)	Mortality	02	-
Treatment / Experiment Phase (Day 0)	Mortality	-	0/2

Clinical Signs

No abnormal clinical signs were observed in any of the animals before and during the experimental duration.

Table No 6. Clinical Signs

Days of Observation									
Animal Number	Acclimatization							Animal Number	Treatment
	1	2	3	4	5	6	7		0
96964	1	1	1	1	1	1	1	P1	1
96966	1	1	1	1	1	1	1	P2	1

Note: 1- Normal

Body Weight

- On treatment day (Day 0):
- Body weight of P1: 54.2 kg
- Body weight of P2: 70.1 kg

Table No 7. Individual Body Weight

Animal Number	Sex	Treatment (Day 0)
P1	Female	54.2 kg
P2	Female	70.1 kg

Note: kg- Kilograms.

Clinical Pathology

- Standard haematology and clinical chemistry tests were performed on blood samples pre and post-implantation.
- Haematology/biochemistry showed no difference or abnormal values between pre- and post-procedural samplings.

Euthanasia

- Immediately after the completion of the procedure, the animals were humanely euthanized by thiopentone (100 mg/kg) injection in the marginal ear vein.

Necropsy

- Gross necropsy and photography were done for the organs of the test item implantation with downstream organs to assess the local effect of thrombus formation.
- Freshly necropsied photography was done first for the Extra Long device in situ and then on explant to examine and document regional device-contacting areas for any vascular device-associated clot and downstream vascular findings.
- A similar assessment on explants was conducted at the thoracic descending aorta where the other two devices were placed.
- Scores for thrombus on or in the withdrawn test item using the Anticoagulated Vessel Implant-score were assigned as per the scoring schema A of ISO 10993-4:2017.
- The score was observed to be zero (0), indicating no thrombosis at the site of insertion.
- The organs underwent a full gross evaluation, with particular attention to evidence of thromboembolism or other abnormalities.
- No abnormal gross findings were observed in any of the tissues examined.
- Images are provided in Necropsy image P2.

V. Conclusion

The study concluded that the Long introducer sheath is safe and effective, demonstrating no thrombogenic activity in a swine model. The device successfully reached the target region of the pulmonary artery and supported related procedures, including the navigation of the balloon and Navigator delivery device for pulmonary valve deployment. Angiographic imaging confirmed good patency with no evidence of thrombus formation during the dwelling period. Post-procedural necropsy revealed no thrombus formation or injury to the luminal interface of the pulmonary artery, iliofemoral vein, or inferior vena cava. Hematology and clinical chemistry parameters showed no significant differences before and after the procedure. The Anticoagulated Vessel Implant scoring scheme score was 0, indicating no significant thrombosis. The device demonstrated

thromboresistance in both regional and downstream areas, with no adverse events or safety concerns. The use of an extra-long sheath in this study provided significant advantages, including improved reach to distal target areas, enhanced support for complex procedures, and increased safety by reducing thrombotic risks. In contrast, conventional sheaths may not reach certain target areas and could pose a higher risk of thrombosis or injury, particularly during prolonged or complex procedures. The customizability of the extra-long sheath for various device sizes further underscores its versatility and utility in diverse clinical scenarios. These benefits highlight why the extra-long sheath was chosen for this application, offering a reliable solution for challenging vascular interventions.

References

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