ClinicalTrials.gov
Cover Page

CLINICAL INVESTIGATIONAL PLAN

REGAL

A Real World Evaluation of the ELUVIA Drug Eluting Stent in All-Comers With Superficial Femoral Artery and Proximal Popliteal Artery Disease

NCT Number: NCT03037411

CIP nr: S2346

VERSION: 1.0

DATE: 08 August 2016

CLINICAL INVESTIGATIONAL PLAN

REGAL

A Real World Evaluation of the ELUVIA™ Drug ElutinG Stent in All-Comers with SuperficiaL Femoral Artery and Proximal Popliteal Artery Disease.

CIP nr: S2346

VERSION: 1.0

DATE: 08 August 2016

Sponsored By:

Boston Scientific International SA

Le Val Saint Quentin
2 Rue René Caudron
78960 Voisins-Le-Bretonneux
France

Supported By:

genae Group

Justitiestraat 6B
2018 Antwerp
Belgium

TABLE OF CONTENTS

1. CLINICAL INVESTIGATIONAL PLAN (CIP) APPROVAL PAGE

Study Title	A Real World Evaluation of the ELUVIA™ Drug ElutinG Stent in All-Comers with Superficial FemoraL Artery and Proximal Popliteal Artery Disease **(REGAL)**
CIP Number	S2346
CIP Version	1.0
CIP Date	08 August 2016

10 Aug 2016

Prof. Dr. Carlo Setacci — Date

Coordinating Clinical Investigator

10 Aug 2016

Lieve Cornelis — Date

Clinical Trial Manager

Sponsor representative

10 Aug 16

Evi Petro, PhD — Date

Clinical Project Manager, genae Belgium

Author

1. CLINICAL INVESTIGATIONAL PLAN (CIP) APPROVAL PAGE

Study Title	A Real World Evaluation of the ELUVIA™ Drug ElutinG Stent in All-Comers with Superficial FemoraL Artery and Proximal Popliteal Artery Disease **(REGAL)**
CIP Number	S2346
CIP Version	1.0
CIP Date	08 August 2016

Prof. Dr. Carlo Setacci — Date

Coordinating Clinical Investigator

Lieve Cornelis — Date

Clinical Trial Manager

Sponsor representative

Evi Petro, PhD — Date

Clinical Project Manager, genae Belgium

Author

2. CIP SIGNATURE PAGE

Study Title	A Real World Evaluation of the ELUVIA™ Drug ElutinG Stent in All-Comers with Superficial FemoraL Artery and Proximal Popliteal Artery Disease **(REGAL)**
CIP Number	S2346
CIP Version	1.0
CIP Date	08 August 2016

I have reviewed this protocol and agree to adhere to the requirements and responsibilities listed herein. I am trained to the contents of this protocol, percutaneous angioplasty procedures, and the specific use of the device listed in this protocol. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practices, Declaration of Helsinki, the International Standard ISO 14155:2011 and all applicable regulatory requirements.

_____ _____

Site Principal Investigator Name (please print or use stamp) Site Number

_____ _____

Site Principal Investigator Signature Date

3. CIP EXECUTIVE SUMMARY

PROTOCOL TITLE: A Real World Evaluation of the ELUVIA™ Drug ElutinG Stent in All-Comers with SuperficiaL Femoral Artery and Proximal Popliteal Artery Disease **(REGAL)**

<table>
<tr><td>CIP Short title</td><td>REGAL</td></tr>
<tr><td>CIP number</td><td>S2346</td></tr>
<tr><td>Sponsor</td><td>Boston Scientific Corporation</td></tr>
<tr><td>Objective</td><td>To collect additional data including health economics data to support the use of the ELUVIA Drug-Eluting Vascular Stent System (ELUVIA Stent) for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions.</td></tr>
<tr><td>Indication(s) for Use</td><td>The ELUVIA Stent System is intended to improve luminal diameter in the treatment of symptomatic de novo or restenotic lesions in the native SFA and/or PPA with reference vessel diameters (RVD) ranging from 4.0-6.0 mm.</td></tr>
<tr><td>Device</td><td>The ELUVIA Stent is a paclitaxel-eluting, self-expanding nitinol stent developed on the same stent and delivery system as the BSC Innova™ Vascular Self-Expanding Stent System.</td></tr>
<tr><td>Device Sizes</td><td>ELUVIA Stent
<table>
<tr><td>Stent Diameter (mm)</td><td>Stent Length (mm)</td><td>Recommended Vessel Diameter (mm)</td></tr>
<tr><td>6</td><td>40, 60, 80, 100, 120, 150</td><td>4.0 – 5.0</td></tr>
<tr><td>7</td><td>40, 60, 80, 100, 120, 150</td><td>5.0 – 6.0</td></tr>
</table>
The ELUVIA Stent is available in two stent delivery system (SDS) sizes; 75 cm and 130 cm. The sheath compatibility is 6 French used with 0.035 inch guidewires.</td></tr>
<tr><td>Study Design</td><td>A European, prospective, multi-center Post-Market Clinical Follow-up (PMCF) trial providing additional data including health economics data to support the use of the ELUVIA stent in the treatment of lesions located in the femoropopliteal arteries.</td></tr>
<tr><td>Study Assessments</td><td>• Health Economics:
o Walking Improvement and Quality of Life Improvement at 1 month, 6 months, 12 months and 24 months as assessed by change in Walking Impairment Questionnaire (WIQ) and EQ-5D-5L™ from baseline
o Health care costs associated with index procedure
o Changes in healthcare utilization over time and associated health care costs
o Rate of Primary and Secondary Sustained Clinical Improvement at 1 month, 6 months, 12 months and 24 months as assessed by changes in Rutherford Classification from baseline</td></tr>
</table>

	○ Rate of Hemodynamic Improvement at 1 month, 6 months, 12 months and 24 months as assessed by changes in Ankle-Brachial Index (ABI) from baseline • Technical success • Procedural success • Major Adverse Event (MAE) rate (and individual components) at each follow-up visit, defined as all causes of death, target limb major amputation and/or Target Lesion Revascularization (TLR) • Primary Patency and Assisted Primary Patency at 6 months, 12 months and 24 months assessed by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVRs). Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the DUS PSVR is ≤ 2. 4 at the follow-up visit in the absence of clinically-driven TLR or bypass of the target lesion. All DUS readings will be assessed by an independent core laboratory. • Clinically-driven TLR and clinically-driven TVR Rate at each follow-up visit • Adverse Event Rates (unanticipated, major, serious, device/procedure-related) at each time point • Distribution of Rutherford Class during follow-up as compared to baseline at 1 month, 6 months, 12 months and 24 months
Population	500 subjects to receive treatment with the ELUVIA Drug Eluting Stent. Up to 30 study centers in up to 10 European countries may enroll subjects in the study.
Study Duration	It is expected that the enrollment will take approximately 12 months. Subject participation will last approximately 2 years. The trial will be considered complete after all subjects have completed the 24 month (2 year) follow-up visit, were discontinued or withdrawn prior to the 24 month (2 year) follow-up visit, have died, or the last 24 month (2 year) follow-up visit window is closed. It is estimated that it will take approximately 4 years to complete this trial.
Inclusion Criteria	1. Subjects age 18 and older 2. Subject is willing and able to provide written consent before any study-specific test or procedure is performed, and agrees to attend all follow-up visits 3. De novo, restenotic or (re)occluded lesions in the native femoro-popliteal arteries, with reference vessel diameter (RVD) ranging from 4.0-6.0 mm, suitable for endovascular treatment
Exclusion Criteria	1. Subject is pregnant or planning to become pregnant during the course of the study 2. Life expectancy of less than 1 year (which is defined as documented life expectancy less than 12 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the clinical follow-up, limit the subject's compliance with the standard of care follow-up, or impact the scientific integrity of the trial) 3. Known allergy to the ELUVIA stent system or any of its components,

	concomitant medication, contrast agents (that cannot be medically managed), 4. Subject enrolled in an investigational study that has not reached primary endpoint at the time of enrollment or that clinically interferes with the current study assessments (Note: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies)
Informed Consent Process and Point of Enrollment	Once the subject has signed the approved Informed Consent Form (ICF), and has met all inclusion and no exclusion criteria, the subject will be considered eligible to be enrolled in the study. If the subject is found to not meet the inclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be included in the study, nor should the subject be followed post-procedure per protocol. A subject is considered enrolled when the ELUVIA stent system is advanced into the patient's vasculature.
Follow-up Schedule	Subject evaluation is recommended at following time points post-procedure, but is dependent on the local standard of care follow-up schedule: • 1 month: 30 days -15 days to +60 days (Day 15 – 90), • 6 months: 182 days ±91 days (Day 91 – 273), • 12 months: 365 days ±91 days (Day 274 – 456), and • 24 months: 730 days -273 days to +30 days (Day 457 – 760) Subjects who are enrolled but an ELUVIA stent was not successfully implanted will be followed through the 1-month follow-up visit only. Data for assessment of MAE will be collected for these subjects; other testing is not required. All follow-up visits will be conducted in the office/clinic as per standard of care. <u>Planned protocol-required testing</u> includes the following: • Angiography during the index procedure to assess technical success and procedural success. • DUS at 6 months, 12 months (1 year) and 24 months (2 years) to assess lesion and vessel patency, as per standard of care. • Walking Impairment Questionnaire (WIQ) at 1 month, 6 months, 12 months (1 year) and 24 months (2 years) visits to assess Walking Ability. • EQ-5D-5L™ at 1 month, 6 months, 12 months (1 year) and 24 months (2 years) to assess Quality of Life. • Rutherford Categorization, as per standard of care • ABI Measurements, as per standard of care
Required Medication	Investigators are recommended to prescribe concomitant anti-coagulant and anti-platelet medications consistent with current local clinical practice. Antiplatelet and

Therapy	anti-coagulant medication usage will be collected and reported for the duration of the trial.
Statistical Methods	No formal tests of hypotheses are proposed for the REGAL assessments. Statistical comparisons may be performed for exploratory purposes.
Analysis Subgroups	Additional exploratory analysis of all assessments may be performed for the following subgroups: • Age and gender • Co-morbidities (e.g. diabetes, renal insufficiency, etc.) • Peripheral Artery Disease classification (e.g. ABI, Rutherford, etc.) • Lesion location (e.g. proximal, mid, distal SFA, PPA, etc.) • Type of stenosis (e.g. de novo, restenotic, etc.) • Lesion length, degree of stenosis, calcification • TASC classification • Lesion preparation (e.g. scoring balloons, cutting balloons, atherectomy devices, etc.) • Bail out stent implantation (diameter, length, stent size etc.) • Treatment approach (e.g. sub-intimal, intra-luminal, etc.) • QoL (e.g. pain level, WIQ)

4. ASSESSMENT AND FOLLOW-UP SCHEME

Data collection schedule per standard of care							
	Pre-procedure[2]	**During Index Procedure Day 0**	**Pre-Discharge**	**1MFU (Day 15-90)**	**6MFU (Day 91-273)**	**12MFU (Day 274-456)**	**24MFU (Day 457-760**
Informed Consent[1]	X						
In/exclusion criteria	X	X					
Demographics & Medical History, Height and Weight	X						
Serum Creatinine	X						
Platelet count	X						
Pregnancy test[2]	X						
ABI	X			X[3]	X	X	X
RCC (Rutherford-Becker clinical classification)	X			X	X	X	X
WIQ	X			X	X	X	X
EQ-5D-5L	X			X	X	X	X
DUS[4]					X	X	X
Health Economics		X		X	X	X	X
Medication	X	X	X	X	X	X	X
Adverse Events[5]	X	X	X	X	X	X	X

1. Subject's consent obtained and informed consent form signed prior to any study-specific tests or procedures
2. Performed within 30 days of procedure, except urine or blood pregnancy test required for females of childbearing potential performed within 7 days of procedure
3. ABI measurement may be collected immediately post-procedure through 1 Month Follow-up window (Day 0 – 90)
4. DUS images will be sent to the respective core lab for analysis. Follow-up ultrasounds will not be required for any subject who underwent bypass surgery of the target lesion during the 24-month follow-up timeframe, or has a documented occluded stent.
5. Reporting required through the end of study for UADEs and (S)ADEs/Device Deficiencies.

5. CONTACT DETAILS

Contact information is provided below. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the sites and committees as needed.

Coordinating investigator	**Prof. Dr. Carlo Setacci** Policlinico Santa Maria alle Scotte di Siena Viale Mario Bracci 13 53100 Siena, Italy
Sponsor	**Boston Scientific International SA** Le Val Saint Quentin 2 Rue René Caudron 78960 Voisins-Le-Bretonneux France
Study contact	**Evi Petro** genae Belgium nv Justitiestraat 6B 2018 Antwerp, Belgium Evi.petro@genae.com **Lieve Cornelis** Boston Scientific, Peripheral Interventions, Clinical Green Square, Lambroekstraat 5D 1831 Diegem, Belgium Lieve.cornelis@bsci.com
CRO, Data Management, Regulatory & Safety	**genae group** Justitiestraat 6B 2018 Antwerp, Belgium
Core Lab	**corelab Black Forest GmbH** Südring 15 79189 Bad Krozingen Germany

List of principal investigators and investigation sites will be maintained separately and is available upon request.

6. INTRODUCTION AND RATIONALE

6.1 Background

Peripheral Arterial Disease (PAD) is the third leading cause of cardiovascular morbidity after myocardial infarction (MI) and stroke. Over the past decade, percutaneous catheter-based techniques have improved such that acute procedural success is high even in complex anatomy. This has led to the adoption of endovascular treatment as the first strategy treatment in PAD-patients.

The femoropopliteal segment is a challenging vascular territory and has been among the least effective of all endovascular procedures in terms of long-term patency[1,2,3]. In recent years, however, improvements in device technology and the skill-sets of the interventionalists have facilitated the treatment of complex lesions, including long-segment chronic occlusions with or without moderate calcification. More specific, the application of self-expanding nitinol stent technology seemed to improve the safety and durability of stenting in the SFA due to its unique properties such as flexibility, persistent radial force when oversized to a vessel, and ability for crush recovery in these high flexion and torsion force areas in the femoropopliteal arteries[1,4,5,6]. In addition, self-expanding nitinol stents are not as prone to external compression as are balloon-expandable stents.

Although above the knee use of nitinol Bare Metal Stents (BMS) is safe and feasible, it is evidently associated with significant neointimal hyperplasia and early restenosis,[7,8] which may be due to the chronic external forces on the vessel/stent interface resulting in a chronic stimulus for restenosis[9]. Therefore, the interest of investigators turned towards pharmaceuticals such as paclitaxel to suppress neointimal growth and restenosis after stent deployment. DES technology was developed to prevent early thrombosis and late luminal loss to potentially improve long-term patency rates for SFA[10].

6.2 ELUVIA Stent System

Boston Scientific Corporation (BSC) developed the ELUVIA stent, a paclitaxel-eluting, self-expanding nitinol stent, for use in the femoropopliteal arteries.

The ELUVIA Stent System leverages many successful BSC programs with global commercial approval for safe and efficacious use in subjects, and received CE-mark in February 2016. The ELUVIA stent and Stent Delivery System (SDS) is leveraged from the Innova™ Stent System, the drug coating polymers are leveraged from the PROMUS Element/PROMUS Element Plus Stent System, while the active pharmaceutical compound (paclitaxel) is leveraged from the TAXUS Element/ION Stent System.

6.3 MAJESTIC First Human Use Study

The MAJESTIC clinical study was the first BSC clinical study with the ELUVIA stent system.

Enrollment was completed in March 2014, The primary effectiveness endpoint of primary patency at nine months was 94.4%, with a one-sided lower 95% confidence bound of 86.3% that exceeded the performance goal of 75%. The nine-month composite MAE rate was 3.6%.

The 3.6% MAE rate consisted of two TLR events through 9 months, with no all-cause death through 1 month, and no target limb major amputation through 9 months. At 12 months, primary patency was 96.1% and the MAE rate was 3.8%; both MAEs were TLRs. No stent fractures were identified.

The MAJESTIC results showed that patients whose femoropopliteal arteries were treated with the Eluvia stent sustained a high patency and low MAE rate through 12 months.

The study is currently in long term follow up and is expected to be complete in 2017.

6.4 IMPERIAL IDE Study

IMPERIAL is a global, prospective, multi-center trial evaluating the safety and effectiveness of the ELUVIA stent versus the Zilver PTX stent. The trial consists of a prospective, multicenter, 2:1 randomized (ELUVIA vs Zilver PTX), controlled, single-blind, non-inferiority trial (RCT), a concurrent, non-blinded, non-randomized, single-arm, pharmacokinetic (PK) substudy and a concurrent, non-blinded, non-randomized, single-arm Long Lesion substudy.

Approximately 527 - 535 subjects will be enrolled in the IMPERIAL trial.

Up to 75 study centers worldwide will enroll subjects in the RCT. Regions participating include the United States, Canada, European Union, Japan and New Zealand.

The study is currently in the enrollment phase and is expected to be complete in 2022.

6.5 EMINENT Post-Market Study

EMINENT is a prospective, multi-center study confirming the superior effectiveness of the ELUVIA stent versus Self-Expanding Bare Nitinol Stents. The study is a 2:1 randomized (ELUVIA vs Self-Expanding Bare Nitinol Stents), controlled, single-blind, superiority trial (RCT).

750 subjects will be enrolled in the EMINENT trial. Up to 75 study centers in up to 10 European countries may enroll subjects in the study.

The study is currently in the start-up phase and is expected to be complete in 2021.

6.6 Clinical trial data ELUVIA Stent System

There is a large set of clinical data available for devices from which components have been leveraged for the ELUVIA Stent System. Successful results have been seen to date demonstrating safety and effectiveness for a variety of indications in coronary and peripheral artery stenosis. The first results of the ELUVIA Stent System (MAJESTIC study) demonstrate a favorable effectiveness and safety profile.

Overall, the ELUVIA stent based on the Innova stent platform with additional paclitaxel coating is intended to reduce restenosis and improve long-term vascular patency and quality of life (QOL) compared to balloon angioplasty, balloon expandable stents, and nitinol BMS.

7. OBJECTIVE

The objective of the REGAL study is to collect additional data including health economics data to support the use of the ELUVIA Drug-Eluting Vascular Stent System (ELUVIA Stent) for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions.

8. STUDY ASSESSMENTS

The following study assessments will be assessed during the course of the REGAL study:

- Health economics:
  - Walking Improvement and Quality of Life Improvement at 1 month, 6 months, 12 months and 24 months as assessed by change in Walking Impairment Questionnaire (WIQ) and EQ-5D-5L™ from baseline
  - Health care costs associated with index procedure
  - Changes in healthcare utilization over time and associated health care costs
  - Rate of Primary and Secondary Sustained Clinical Improvement at 1 month, 6 months, 12 months and 24 months as assessed by changes in Rutherford Classification from baseline
  - Rate of Hemodynamic Improvement at 1 month, 6 months, 12 months and 24 months as assessed by changes in Ankle-Brachial Index (ABI) from baseline
- Technical success
- Procedural success
- Major Adverse Event (MAE) rate (and individual components) at each follow-up visit, defined as all causes of death, target limb major amputation and/or Target Lesion Revascularization (TLR)
- Primary Patency and Assisted Primary Patency at 6 months, 12 months and 24 months assessed by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVRs). Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the DUS PSVR is ≤ 2.4 at the follow-up visit in the absence of clinically-driven TLR or bypass of the target lesion. All DUS readings will be assessed by an independent core laboratory.
- Clinically-driven TLR and clinically-driven TVR Rate at each follow-up visit
- Adverse Event Rates (unanticipated, major, serious, device/procedure-related) at each follow-up visit
- Distribution of Rutherford Class during follow-up as compared to baseline at 1 month, 6 months, 12 months and 24 months

9. STUDY DESIGN

The REGAL study is a European, prospective, multi-center Post Market Clinical Follow-up (PMCF) trial providing additional data including health economics data to support the use of the ELUVIA stent in the treatment of lesions located in the femoropopliteal arteries.

The ELUVIA stent is CE-marked and commercially available in the regions included in this study, and has already demonstrated its safety and effectiveness for treatment of

symptomatic de-novo or restenotic lesions in the native superficial femoral artery (SFA) and/or proximal popliteal artery (PPA) with reference vessel diameters (RVD) ranging from 4.0-6.0 mm.

9.1 Scale and Duration

500 subjects will be enrolled in the REGAL study to receive treatment with the ELUVIA Stent system.

The study will be conducted in up to 30 study centers in up to 10 European countries.

All subjects will be screened according to the protocol inclusion and exclusion criteria and will be considered eligible to be enrolled in the study once a signed informed consent form is in place.

If the subject is found to not meet the inclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be included in the study, nor should the subject be followed post-procedure per protocol.

A subject is considered enrolled when the ELUVIA stent system is advanced into the patient's vasculature.

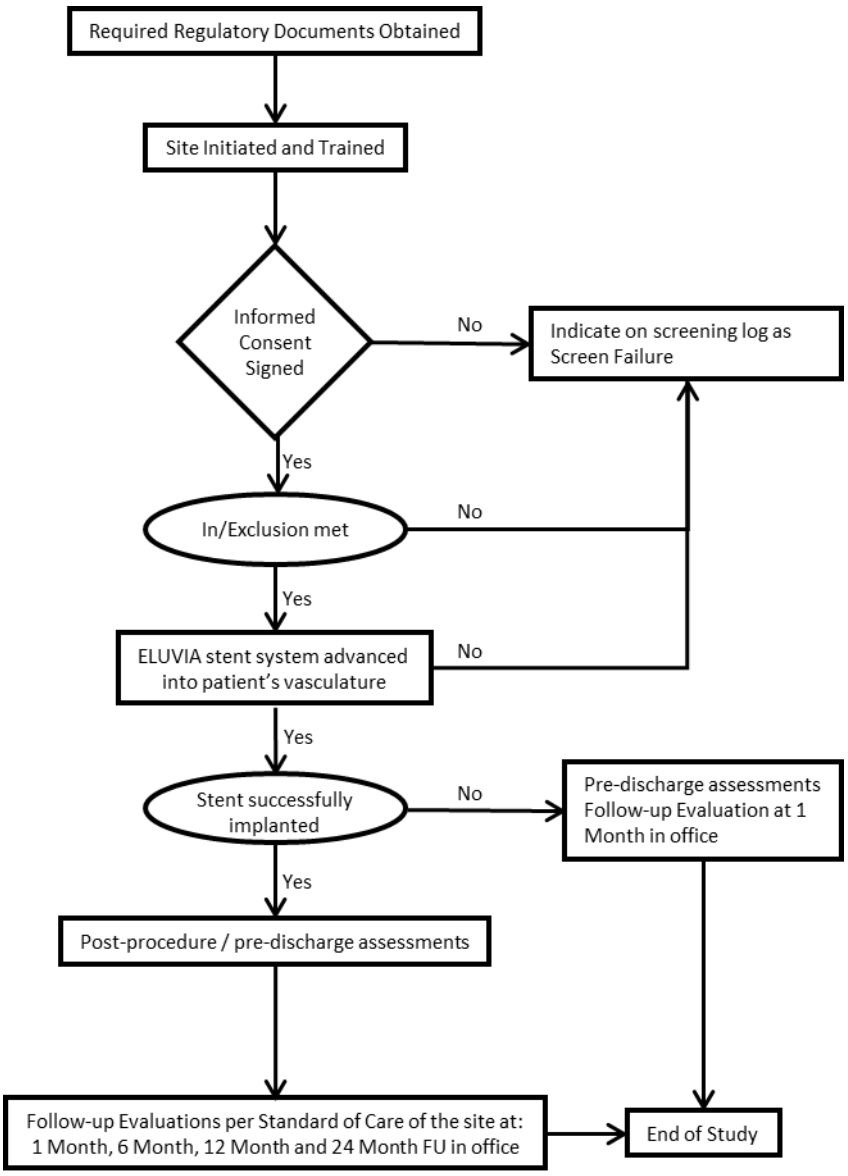
Clinical follow-up is required as per standard of care and data will be collected at the following time points: pre-discharge, 1 month, 6 months, 12 months and 24 months post index procedure.

Subjects who are enrolled but an ELUVIA stent was not successfully implanted will be followed through the 1-month follow-up visit only. Data for assessment of MAE will be collected for these subjects; other testing is not required.

The enrollment period is expected to last approximately 12 months. No investigative site will be allowed to enroll more than 20 percent (100 subjects) of the total study population. The study will be considered complete after all subjects have completed the 24 month (2 year) follow-up visit, were discontinued prior to the 24 month (2 year) follow-up visit, have died, or the last 24 month (2 year) follow-up visit window is closed.

It is estimated that it will take approximately 4 years to complete this study.

9.2 Study Flow Chart



10. STUDY POPULATION

10.1 Subject Selection

The Intended population for the REGAL study are 'real world'-patients with symptomatic de-novo, restenotic, or (re)occluded lesions in the native superficial femoral artery (SFA) and/or proximal popliteal artery with reference vessel diameter (RVD) ranging from 4.0-6.0 mm, suitable for endovascular treatment.

10.2 Inclusion Criteria

For inclusion in the study subjects must fulfil **ALL** of the following criteria:

1. Subjects age 18 and older
2. Subject is willing and able to provide written consent before any study-specific test or procedure is performed and agrees to attend all follow-up visits
3. De novo, restenotic or (re)occluded lesions in the native femoro-popliteal arteries, with reference vessel diameter (RVD) ranging from 4.0-6.0 mm, suitable for endovascular treatment

10.3 Exclusion Criteria

Subjects are excluded if **ANY** of the following criteria are met:

1. Subject is pregnant or planning to become pregnant during the course of the study
2. Life expectancy of less than 1 year (which is defined as documented life expectancy less than 12 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the clinical follow-up, limit the subject's compliance with the standard of care follow-up, or impact the scientific integrity of the trial)
3. Known allergy to the ELUVIA stent system or any of its components, concomitant medication, contrast agents (that cannot be medically managed)
4. Subject enrolled in an investigational study that has not reached primary endpoint at the time of enrollment or that clinically interferes with the current study assessments (Note: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies)

11. DEVICE DESCRIPTION

11.1 ELUVIA Drug-Eluting Stent System

The ELUVIA stent system is manufactured by Boston Scientific Corporation and comprised of the implantable endoprosthesis and the stent delivery system (SDS). The stent is a laser cut self-expanding stent composed of a nickel titantium alloy (nitinol). On both the proximal and distal ends of the stent, radiopaque markers made of tantalum increase visibility of the stent to aid in placement. The stent is constrained within a 6F delivery system. The delivery system is a triaxial design with an outer shaft to stabilize the stent delivery system, a middle

shaft to protect and constrain the stent, and an inner shaft to provide a guidewire lumen. The delivery system is compatible with 0.035 in (0.89 mm) guidewires.

The ELUVIA stent system carries a drug/polymer coating formulation consisting of paclitaxel (the active ingredient), and PVDF-HFP Polymer Carrier (the inactive ingredient).

CE-mark for the ELUVIA stent system was obtained in February 2016.

11.1.1 Paclitaxel Drug

The active pharmaceutical ingredient is semi-synthetic paclitaxel. Semi-synthetic paclitaxel is synthesized from precursor compounds isolated from a spectrum of Taxus species and hybrids.

11.1.2 Primer Polymer and Drug Matrix Copolymer Carrier

The ELUVIA stent contains a primer polymer layer PBMA - poly (n-butylmethacrylate) between the bare metal stent and drug matrix layer. The drug matrix layer is comprised of a semi-crystalline random copolymer, PVDF – HFP - poly(vinylidene fluoride-co-hexafluoropropylene), blended with paclitaxel.

11.1.3 ELUVIA Stent System Product Description

Characteristic	ELUVIA Stent System
Stent material	Nitinol
Drug product	Paclitaxel
Nominal Paclitaxel Content Range (based on stent length and diameter)	0.167µg/mm^2
Polymer(s)	Primer Layer: poly(n-butyl methacrylate) (PBMA) Active Layer: poly (vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP)
Delivery working length	75 cm, 130 cm
Stent delivery system (SDS)	6 F tri-axial system
Catheter shaft outer diameter	0.080 +/- 0.002”
Stent strut thickness	0.0039“ strut width, 0.0086“ strut wall thickness

11.1.4 ELUVIA stent Sizes

The ELUVIA stent is available in a variety of diameters and lengths. The delivery system is offered in two working lengths (75 cm and 130 cm). The ELUVIA stent matrix included in the REGAL Study is summarized in the below table.

SDS size	ELUVIA Stent sizes (mm)
75 cm	6.0 x 40, 6.0 x 60, 6.0 x 80, 6.0 x 100, 6.0 x 120, 6.0 x 150

SDS size	ELUVIA Stent sizes (mm)
130 cm	6.0 x 40, 6.0 x 60, 6.0 x 80, 6.0 x 100, 6.0 x 120, 6.0 x 150
75 cm	7.0 x 40, 7.0 x 60, 7.0 x 80, 7.0 x 100, 7.0 x 120, 7.0 x 150
130 cm	7.0 x 40, 7.0 x 60, 7.0 x 80, 7.0 x 100, 7.0 x 120, 7.0 x 150

11.2 Device Accountability

Since the ELUVIA stent is a commercially available CE-marked device, all devices used within the study will be used off-the-shelf. The Investigator must ensure that the device is used only in accordance with the Directions for Use (DFU).

The Principal Investigator or an authorized designee shall keep records documenting the use of the ELUVIA stent, which shall include the following information for each device used (lot number or unique code):

- Stent diameter and stent length
- Date of use
- Subject identification

Written procedures for device accountability may be required by national regulations.

12. METHODS

The data collection schedule for the REGAL study is summarized in section 4.

12.1 Screening

A Screening and Enrollment Log will be maintained by each investigational site to document selected information about all subjects who meet (or fail to meet) the REGAL trial eligibility criteria, including the reason for screen failure.

Study investigators are expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

12.2 Informed Consent

Prior to collection of any of the subject’s data, a signed informed consent form must be obtained from every subject using the most recently approved ICF.

The process of obtaining informed consent must be consistent with the Declaration of Helsinki. The investigator or responsible medical staff (as allowed per national law) will explain the nature, purpose and risks of the study and provide the subject with a copy of their personally signed and dated informed consent form (ICF).

The person obtaining consent will avoid any coercion or undue improper influence on or inducement of the subject to participate. They will not waive or appear to waive the subject's legal rights. They will use native non-technical language that is understandable to the subject. The refusal of a subject to participate in the study or a subject's decision to withdraw from the study must never interfere with the patient-doctor relationship.

The subject will be given sufficient time to ask questions, to receive answers and to consider the implications of study participation before making a decision and thus before signing the consent document.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, catheterization may demonstrate that the subject is not a suitable candidate for the trial. Should there be any amendments to the Clinical Investigational Plan (CIP), which would directly affect the subjects' participation in the study, e.g. a change in any significant patient-facing procedure, the ICF must be amended to incorporate this modification and all subjects must agree to sign this amended ICF to confirm that they re-consent to continue their participation in the study.

The original signed copy of the subject's ICF must be maintained in the study files. The subject should receive a copy of the signed ICF. The consent process and subject's study participation should be documented in the patient's medical records.

12.3 Point of Enrollment

Once the subject has signed the Informed Consent Form, and has met all inclusion and no exclusion criteria, the subject will be considered eligible to be enrolled in the study.

If the subject is found to not meet the inclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be enrolled, nor should the subject be followed post-procedure per protocol. A subject is considered enrolled when the ELUVIA stent system is advanced into the patient's vasculature.

12.4 Study Assessments and Measurements

12.4.1 Pre-Procedure Assessments – Up to 30 Days prior to Day 0

The following pre-procedure data will be collected within 30 days prior to the index procedure (unless otherwise specified) for all subjects:

- Demographics and medical history
- Physical assessment including:
    - Weight and height
    - Rutherford Category Assessment
    - Ankle-Brachial Indices (ABI) measurements
- Laboratory tests
    - Serum creatinine
    - Platelet Count
- Confirmation that all inclusion/exclusion eligibility criteria have been met
- Administer Questionnaire Assessments
    - Walking Impairment Questionnaire (WIQ)
    - EQ-5D-5L

12.4.2 Pre-Procedure Assessments – Up to 7 Days prior to Day 0

The following pre-procedure data will be collected within 7 days prior to the index procedure (unless otherwise specified) for all subjects:

- Pregnancy test for females of childbearing potential with analysis per local practice (serum and/or urine)
- Antiplatelet medication usage (if applicable)

12.4.3 Procedure – Day 0

Investigators will manage the cardiovascular risk factors and comorbidities for all subjects according to standard care. Investigators should ensure close monitoring of the amount of contrast for subjects with elevated serum creatinine levels and consider preventive measures (medication and hydration) to reduce the risk of contrast-induced nephropathy (CIN).

Diagnostic angiography of the lower extremities should be performed using standard techniques. Visual angiographic assessment may be used to determine if criteria are met.

Treatment of Target Lesion

The start of the index procedure is defined as the time of guide catheter insertion into the sheath for the SFA/PPA interventional procedure. The target lesion will be treated per DFU.

Procedural recommendations

Use of a radiopaque ruler or other standard is recommended to help with calibration. Optimal target lesion/vessel preparation is recommended.

Pre-dilation of the target lesion with optimally sized balloon(s) (nominal size of artery) is recommended before stent placement, but is at the discretion of the implanting Investigator. Record the following information on pre-dilation balloon(s) used:

- Maximum balloon diameter (mm) inflated
- Maximum pressure (atmospheres) inflated
- Maximum length of time (seconds) inflated

After stent placement, the Investigator should ensure that the stent is in full contact with the arterial wall. In order to achieve full contact, post-dilatation may be performed at the discretion of the Investigator. Record the following information on post-dilation balloon(s) used:

- Maximum balloon diameter (mm) inflated
- Maximum pressure (atmospheres) inflated
- Maximum length of time (seconds) inflated

Peri-stent dissections should be treated conservatively, with low pressure prolonged balloon inflation, or with additional study stent implantation per standard practice. Haziness, lucency, or filling defects within or adjacent to the stent, and angiographic complications such as distal thromboemboli or no reflow, should also be treated per standard practice. All angiographic complications that occur should be documented by angiography.

ELUVIA

Prior to use of the ELUVIA stent, the treating physician must carefully read and be familiar with the entire DFU. The ELUVIA DFU must be followed for implanting the ELUVIA stent. Anticoagulant therapy should be consistent with guideline practices and the hospital standard of practice during the procedure.

NOTE: If a second or third stent is required due to complications (e.g., dissection, misplacement or under-sizing of the target lesion), the additional stent placed should preferably be an ELUVIA stent as well.

End of the Index Procedure

The end of the index procedure is defined as the time the guide (catheter or sheath) is removed (post final angiography). The introducer(s) sheaths should be removed as per standard local practice. The following procedures will be completed:

- Document procedural, target lesion, pre-dilatation, post-dilatation (if applicable), and study stent information on the appropriate eCRFs
- Record antithrombotic medications
- Complete AE assessment

12.5 Post-procedure/Pre-hospital Discharge

The subject may be discharged from the hospital when clinically stable at the Investigator's discretion. The following assessments will be completed prior to hospital discharge:

- Medication assessment
- AE assessment (SADEs, UADEs and ADEs/Device Deficiencies)
- Health care costs associated with index procedure

It is important that trial site personnel review the trial follow-up requirements with the subject to maximize compliance with the follow-up schedule and medication regimen. It is also important that trial site personnel discuss the subject's return for follow-up assessments according to the trial event schedule. It is advised that the study staff schedules a date for the first follow-up visit with the subject at the time of hospital discharge.

12.6 Angiography

All subjects will undergo angiographic assessment during the index procedure per standard of care. Subjects requiring re-intervention of the target vessel during the 24 month follow-up period will undergo angiographic assessment at the time of re-intervention as standard of care.

12.7 Follow-up

All enrolled subjects will be evaluated prior to discharge from the index procedure and at approximately 1 month, 6 months, 12 months and 24 months after the index procedure. Subject evaluation is recommended at these time points, but is dependent on the local standard of care follow-up schedule.

Subjects who underwent advancement of the ELUVIA stent system into the vasculature but a stent was not implanted will be considered enrolled and will be followed for safety through the 1-month follow-up visit only. Data for assessment of MAE will be collected for these subjects; other testing is not required.

The results of the subjects' clinical status and functional testing (Rutherford Categorization and ABI) should be completed prior to initiating the DUS imaging, if required. Subjects requiring re-intervention should be treated according to the Investigator's discretion and standard of care. These subjects should receive an approved, commercially available treatment (if appropriate).

Note: Follow-up ultrasounds will not be required for any subject who underwent bypass surgery of the target lesion during the 24 month follow-up timeframe, or has a documented occluded stent.

Follow-up evaluation is required as per local practice and data will be collected for following assessments:

12.7.1 1-Month Follow-up Visit: Day 15 – 90 (30 days -15 days to +60 days)

During the 1 Month office visit, the following data will be collected:

- Walking Impairment Questionnaire
- EQ-5D-5L Questionnaire
- Healthcare utilization information (including health care costs)
- Adverse Events Assessment (SADEs, UADEs and ADEs/Device Deficiencies)
- Medication Assessment

The following assessments will be performed during the 1 Month office visit, as per local standard of care:

- Rutherford Categorization
- ABI Measurements *(may be collected immediately post-procedure through 1 Month Follow-up window [Day 0 – 90])*

12.7.2 6-Month Follow-up Visit: Day 91 – 273 (182 days ± 91 days)

During the 6 Month office visit, the following data will be collected:

- Walking Impairment Questionnaire
- EQ-5D-5L Questionnaire
- Healthcare utilization information (including health care costs)
- Adverse Events Assessment (SADEs, UADEs and ADEs/Device Deficiencies)
- Medication Assessment

The following assessments will be performed during the 6 Month office visit, as per local standard of care:

- Rutherford Categorization (prior to DUS)
- ABI Measurements (prior to DUS)

- DUS of stented segment performed according to the Core Lab guidelines

12.7.3 12-Month Follow-up Visit: Day 274 – 456 (365 days ± 91 days)

During the 12 Month office visit, the following data will be collected:

- Walking Impairment Questionnaire
- EQ-5D-5L Questionnaire
- Healthcare utilization information (including health care costs)
- Adverse Events Assessment (SADEs, UADEs and ADEs/Device Deficiencies)
- Medication Assessment

The following assessments will be performed during the 12 Month office visit, as per local standard of care:

- Rutherford Categorization (prior to DUS)
- ABI Measurements (prior to DUS)
- DUS of stented segment performed according to the Core Lab guidelines

12.7.4 24-Month Follow-up Visit: Day 457 – 760 (730 days -273 days +30 days)

During the 24 Month office visit, the following data will be collected:

- Walking Impairment Questionnaire
- EQ-5D-5L Questionnaire
- Healthcare utilization information (including health care costs)
- Adverse Events Assessment (SADEs, UADEs and ADEs/Device Deficiencies)
- Medication Assessment

The following assessments will be performed during the 24 Month office visit, as per local standard of care:

- Rutherford Categorization (prior to DUS)
- ABI Measurements (prior to DUS)
- DUS of stented segment performed according to the Core Lab guidelines

12.8 Trial Completion

The trial will be considered complete after all subjects have completed the 24 month (2 year) follow-up visit, were discontinued prior to the 24 month (2 year) follow-up visit, have died or the follow-up visit window is closed.

12.9 Missed or Late Visits

Follow-up-visits are performed per local practice and every effort must be made by the site to retain study subjects for the duration of the study. Missed or late visits are however not considered a protocol deviation if they are not standard of care per the site's patient care policies.

A minimum of 3 attempts (i.e., 2 phone calls followed by a certified letter, or other traceable letter, if necessary) should be made to contact the subject or subject's next of kin for each

missed follow-up visit and this information should be documented in the source. A subject will be considered lost to follow-up after the subject misses 2 consecutive follow-up visits without due cause.

12.10 Medication

Investigators are recommended to prescribe concomitant anti-coagulant and anti-platelet medications consistent with current local clinical practice. Antiplatelet and anti-coagulant medication usage will be collected and reported in the electronic case report form (eCRF) from the time of the pre-procedure visit through the 24 month (2 year) follow-up visit. Additional concomitant medications may be prescribed at the discretion of the treating physician according to standard of care.

12.11 Withdrawal of Individual Subjects

Subjects may leave the study at any time for any reason and without any consequences. The investigator or designee will try to obtain the reason for study withdrawal and document this in the source data.

If a subject chooses to withdraw from the study, no additional data will be collected. The sponsor may retain and continue to use any data collected prior to the withdrawal of consent, unless specified differently by the subject. The subject will return to the care of their chosen physician.

An investigator may discontinue a subject from the study, with or without the subject's consent, for any reason that may, in the Investigator's opinion, negatively affect the well-being of the subject. If a subject is withdrawn from the study, the investigator will promptly inform the subject and sponsor.

12.12 Replacement of Individual Subjects after Early Termination

Subjects who exit the study prematurely will not be replaced.

13. SUSPENSION OR TERMINATION

13.1 Premature Termination of the Study

Early termination of the study is the closure of the clinical study that occurs prior to meeting defined endpoints. Early termination is possible for the whole study or a single site.

Study suspension is a temporary postponement of study activities related to enrollment. Suspension is possible for the whole study or a single site.

Investigators, associated Ethics Committees and regulatory authorities, as applicable, will be notified in writing in the event of study suspension or termination.

13.1.1 Study-wide Termination or Suspension

The sponsor reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection

of subjects. Investigators, associated Ethics Committees (ECs), and regulatory authorities, as applicable, will be notified in writing in the event of study suspension or termination. Possible reasons for premature study suspension or termination include, but are not limited to:

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study
- An enrollment rate far below expectation that prejudices the conclusion of the study
- A decision on the part of the sponsor to suspend or discontinue commercialization of the device

13.1.2 Investigator/Site Termination or Suspension

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial Ethics Committee approval or annual renewal of the study, if applicable
- Persistent non-compliance to the Clinical Investigation Plan (e.g. failure to adhere to inclusion/exclusion criteria)
- Lack of or insufficient enrollment
- Noncompliance to regulations and/or the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow up on data queries and monitoring findings in a timely manner, etc.)
- Ethics Committee suspension of the site
- Fraud or scientific misconduct is discovered
- Investigator request (e.g. no longer able to support the study)

Associated Ethics Committees and regulatory authorities, as applicable, will be notified by the sponsor in writing in the event of investigator/site suspension or termination.

13.1.3 Procedures for Termination or Suspension

A Sponsor-initiated

- Sponsor will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the Regulatory Authority(ies), where required.
- In the case of study termination or suspension for reasons other than a temporary Ethics Committee approval lapse, the investigator will promptly inform the Ethics Committee.
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician (if allowed) of the subjects to ensure appropriate care and follow-up is provided.
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by sponsor and approved by the applicable ethics committees/regulatory authorities.
- In the case of a study suspension, enrolled subjects should continue to be medically followed by the investigator out of consideration of their safety, rights and welfare.

B Investigator-initiated

- The investigator will inform sponsor and provide a detailed written explanation of the termination or suspension at least 30 days prior to the planned termination or suspension.
- The investigator will promptly inform the institution (where required per regulatory requirements).
- The investigator will promptly inform the Ethics Committee and sponsor will promptly inform the Regulatory Authority (where applicable).
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided.
- In the case of a study suspension, subjects enrolled should continue to be medically followed by the investigator out of consideration of their safety, rights and welfare.

C Ethics Committee or Regulatory Authority-initiated

- The investigator will inform sponsor and provide a detailed written explanation of the termination or suspension within 5 business days.
- Subject enrollment must stop until the suspension is lifted.
- Subjects already enrolled should continue to be medically followed in accordance with Ethics Committee/ Regulatory Authority policy.

14. SAFETY

It is the responsibility of the investigator to assess and report to the sponsor, by means of recording in the e-CRF, any event which occurs in any of following categories, after enrollment, whether during or subsequent to the procedure:

- All Device and/or Procedure Related Adverse Events and Serious Adverse Events
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- All Events which meet the per-protocol definition of Major Adverse Event (note: for target limb amputations, both minor and major amputations should be reported)
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the trial.

Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see below for AE definitions).

Refer to the DFU for the known risks associated with the study device(s).

14.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device.

NOTE 1: This definition includes events related to the test device or the comparator
NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan).
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse events will be monitored throughout the study. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse device effect requiring immediate notification to the sponsor or its designated representative.

14.2 Adverse Device Effects

An adverse device effect (ADE) is an AE related to the use of a medical device.

NOTE 1: This definition includes any adverse events resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device.
NOTE 2: This definition also includes any event that is a result of a use error or intentional abnormal use of the medical device.

All reported ADEs will be documented on the appropriate CRF and will include the event description [diagnosis – only signs or symptoms in case underlying diagnosis is not (yet) known], onset, resolution, seriousness, severity, cause and action taken. The investigator must assess causality and severity for all ADEs.

All ADEs will be followed by the Investigator until resolution or until the end of study participation.

14.3 Serious Adverse Events

An adverse event is defined as serious (SAE), whenever the adverse event

a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient hospitalization or prolongation of existing hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness, or
    5) injury or permanent impairment to a body structure or a body function,
c) led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigational Plan, without a serious deterioration in health, is not considered a serious adverse event.

In-patient hospitalization is defined as the subject being admitted to the hospital (≥ 24 hours), with the following exceptions.

- A hospitalization for routine follow-up per standard of care.
- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE or AE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

14.4 Serious Adverse Device Effects

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

14.5 Unanticipated Serious Adverse Device Effects

An unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

14.6 Device Deficiency/Malfunction – Device Specific Events

Device deficiency is the inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Device malfunction means the failure of a medical device to perform in accordance with its intended purpose when used in accordance with the DFU or CIP.

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to the sponsor. If possible, the device(s) should be returned to the sponsor for analysis. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device Deficiencies (DD) (including but not limited to failures, malfunctions, and product nonconformities) and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate eCRF per the study CRF Completion Guidelines. If an AE results from a device deficiency or other device issue, the AE should be reported on the appropriate eCRF.

Device malfunction/failures/deficiencies may or may not result in the subject experiencing harmful effect. All AEs/SAEs associated with a device failure are by definition device-related.

Device deficiencies that did not lead to an AE but could have led to a SAE if:

- either suitable action had not been taken,
- intervention had not been made, or
- circumstances had been less fortunate,

should be reported per the reporting guidelines in the following section.

14.7 Adverse and serious adverse events reporting

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Since the safety reporting requirements and classification systems vary for each Regulatory Authority, requirements from all geographies are taken into account for the collection and reporting of safety information.

Subjects will be carefully monitored during the study for possible adverse events. Any adverse event that occurs after the time of enrollment through end of study participation will be fully evaluated by the Investigator. Appropriate treatment will be initiated and the study follow up will continue as completely as possible.

Causality Assessment

The Investigator must assess the relationship of the AE to the study device (including the medical-surgical procedure) and the occurrence of each adverse event.

Criteria for Assessing Relationship of Study Device or Index Procedure to AE

Classification	Description
Not Related	Relationship to the device or procedure can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the device or the procedure; - the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely Related	The relationship with the use of the device or procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the device or procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible related.
Probably Related	The relationship with the use of the device or procedure seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or with procedure beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with device use/application or procedure; - the event involves a body-site or organ that o the device or procedure are applied to; o the device or procedure have an effect on; - the event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedure and the event.

Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information	• Within 1 business day of first becoming aware[1] of the event. • Reporting required through the end of the study
	Provide source documentation (unidentified) as requested by the Sponsor	• When documentation is available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information	• Within 2 business days of first becoming aware[1] of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide source documentation (unidentified) as requested by the Sponsor	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities)	Complete Device Deficiency CRF with all available new and updated information	• Within 2 business day of first becoming aware[1] of the event and as per local/regional regulations • Reporting required through the end of the study
Adverse Device Effect (Non-Serious)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware[1] of the information

[1]The "become aware date" for an event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event.

Abbreviations: AE=adverse event; CRF=case report form; eCRF=electronic case report form; UADE=unanticipated adverse device effect

Initial reporting may be done by phone, fax, email or by completing the applicable eCRF form with as much information as available at that time. In case of urgent questions regarding safety reporting, please contact the study contact as indicated in section 5 of this Clinical Investigational Plan.

As additional information becomes available, the Investigator will record all ADEs (anticipated and unanticipated) and Device Deficiencies on the appropriate eCRFs.

In case of Major Adverse Events (MAE), copies of source documentation which contain significant information related to the event such as discharge letters, surgery reports, consultation letters, ECGs, laboratory results, etc., and, if applicable, angio and/or DUS images are required for evaluation of the event. Copies of such documentation shall be obtained from the investigator, blinded / de-identified as to the subjects' identity, and provided to the Sponsor or designee.

Regarding subject deaths, it is requested that a copy of the death certificate and a copy of the autopsy report (if applicable), be sent to the sponsor or designee when available. Any other source documents related to the death should also be provided to the sponsor or designee. In the event that no source documents are available, the PI is required to describe the circumstances of the subject's death in a letter, e-mail or other written communication.

UADEs/USADEs have special reporting requirements. The Sponsor will notify the sites, ECs and regulatory bodies as per country specific regulations.

14.8 Annual Safety Report

In addition to the expedited reporting of SADEs, the sponsor will submit, at a minimum once a year throughout the clinical study, an annual safety report to the involved ethics committees and competent authorities of the concerned Member States if required. This annual safety report can be combined with the annual progress report.

14.9 Severity

The investigator will use the following definitions to determine the severity of an adverse event:

- ***Mild:*** Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae.
- ***Moderate***: Interferes with the subject's usual activity and/or requires symptomatic treatment.
- ***Severe***: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

14.10 Clinical Events Committee (CEC)

The CEC is an independent group of individuals with no affiliation with BSC. Committee membership will include practitioners of peripheral endovascular procedures, as well as other experts with the necessary therapeutic and subject matter expertise to review and adjudicate the following endpoints and major adverse events reported by the trial Investigators:

- All Deaths
- Target Lesion Revascularizations
- Target Vessel Revascularizations
- Target limb amputations (major and minor)
- Stent Thrombosis

Responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

15. POTENTIAL RISKS AND BENEFITS

15.1 Risks

Considering the nature and objective of the trial, being a Post-Market Clinical Follow-up study with the primary intention to collect additional data regarding the use of the ELUVIA

stent system, the additional risk associated with participating in this study, is related to the collection of patient data and confidentiality thereof.

The risks associated with the implantation of the ELUVIA stent, CE-marked and commercially available, are described in the current applicable version of the DFU of the ELUVIA stent system.

There may be additional risks linked to the procedure, and follow-up testing which are unforeseen at this time. All assessments planned for the follow-up period are standard of care, with the exception of the quality of life questionnaires (WIQ and EQ-5D-5L), which do not cause any additional risk.

15.2 Risk Minimization Actions

In order to mitigate the risk related to loss of data confidentiality, the study is to be performed in accordance with all applicable data protection laws. All data and information concerning subjects and their participation in this study are considered confidential by the sponsor and its designees. Only authorized Investigators and Sponsor or designated personnel will have access to confidential records. The Ethics Committee and other regulatory authorities also have the right to inspect and copy records pertinent to the study. All public reporting of the results of the study will eliminate identifiable references to subjects.

15.3 Anticipated Benefits

The subject receives treatment of a narrowed upper leg artery and potential improvement in the symptoms of the peripheral artery disease. Furthermore, medical science and future patients may benefit from the results of this study.

15.4 Risk to Benefit Rationale

The ELUVIA stent is a CE-marked device and has been proven to be suitable for its intended purpose. There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed through the provision of the appropriate DFU. Evaluation of the risks and benefits that are expected to be associated with the use of the ELUVIA stent demonstrate that when used under the conditions intended, the benefits associated with the use of the ELUVIA stent should outweigh the risks.

16. STATISTICAL ANALYSIS

The details of all statistical analyses will be described in the Statistical Analysis Plan.

16.1 Sample Size

This study will enroll and treat up to 500 subjects at up to 30 study centers in up to 10 European countries.

16.2 Analysis Population

The intent-to-treat population (ITT) consists of all subjects enrolled in the study in which the ELUVIA stent was implanted. This will be used in the primary analysis of all assessments.
Additionally, all assessments will be analyzed for the per-protocol population (PP). The PP population consists of the subjects enrolled in the study that met all inclusion and exclusion criteria and underwent the procedure (ELUVIA stent implantation).

16.3 Descriptive Statistics

Descriptive statistics will be presented as mean, standard deviation, median, interquartile range (IQR), minimum and maximum for continuous data.
For categorical data, descriptive statistics will be given as the number and percentage of subjects.

16.4 Assessment Analysis

The results for all assessments will be given as descriptive statistics and will not be tested using formal hypotheses.

16.5 Missing Data

All subjects with available data will be used in the statistical analyses. In case of missing data, subjects will be excluded from the specific analysis for which no data is available. No imputation will be performed for missing data.

16.6 Subgroup Analysis

Subgroup analyses may be performed for all assessments for the following subgroups:

- Age and gender
- Comorbidities (e.g. diabetes, renal insufficiency, etc.)
- Peripheral Artery Disease classification (e.g. ABI, Rutherford, etc.)
- Lesion location (e.g. proximal, mid, distal SFA, PPA, etc.)
- Type of stenosis (e.g. de novo, restenotic, etc.)
- Lesion length, degree of stenosis, calcification
- TASC classification
- Lesion preparation (e.g. scoring balloons, cutting balloons, atherectomy devices, etc.)
- Bail out stent implantation (diameter, length, stent size etc.)
- Treatment approach (e.g. sub-intimal, intra-luminal, etc.)
- QoL (e.g. pain level, WIQ, EQ-5D-5L)

16.6.1 Analysis Software

All statistical analyses will be performed using SPSS, version 23 or later (IBM Corp. Released 2014. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

16.6.2 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the primary analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

17. ETHICAL CONSIDERATIONS

17.1 Regulation/Compliance Statement

This study will be performed in accordance with the World Medical Association Declaration of Helsinki, ISO 14155:2011(E) and all local legal and regulatory requirements.

In addition to following the governing regulations, any additional requirements of the individual study site's EC and Regulatory Authority will also be followed by the study site(s) where applicable.

EC and where applicable Regulatory Authority approval for the study is required prior to beginning the study. A copy of the approvals must be sent to the sponsor prior to enrolling the first subject.

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)).

17.2 Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the Clinical Investigation Plan (CIP) / protocol, ISO 14155, ethical principles that have their origin in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following:

- Prior to beginning the study, sign the Clinical Study Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the CIP.
- Provide documentation on his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this CIP, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation.

- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per applicable requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure), per CIP requirements, every SADE and observed DD.
- Report to the sponsor, per the CIP requirements, all SAEs and DD that could have led to a SADE and potential USADE or UADE.
- Report to the EC any SADEs and DD that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this CIP or by the EC, and supply the sponsor with any additional requested information related to the safety reporting of a particular event.
- Ensure that the device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this CIP and local EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in the clinical study in the case of AEs, as described in the ICF.
- Inform the subject of the nature and possible cause of any AEs experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigational site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1 Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3 Ethics Committee

A copy of the written EC, and where appropriate Regulatory Authority approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual EC approval and renewals will be obtained throughout the duration of the study as required by local/country or EC requirements. Copies of the Investigator's reports and the EC continuance of approval must be provided to the sponsor.

17.4 Sponsor Responsibilities

All information and data sent to the sponsor concerning subjects or their participation in this study will be considered confidential by the sponsor. Only authorized sponsor personnel or a sponsor representative including Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by the sponsor for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

The sponsor will keep subjects' health information confidential in accordance with all applicable laws and regulations. The sponsor may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.4.1 Role of Sponsor Representatives

Sponsor personnel can provide technical support to the investigator and other Health Care Personnel (collectively HCP) as needed during stent implant and testing required by the CIP during the index procedure. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of the test device.

Sponsor personnel will not do the following:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- Independently collect critical study data (defined as study endpoint data)
- Enter data in eCRF

18. REIMBURSEMENT AND COMPENSATION FOR SUBJECTS

18.1 Subject Reimbursement

Travel expenses incurred by subjects as a result of participation in the study will be reimbursed if requested in accordance with pertinent country laws and regulations and per the study site's regulations.

18.2 Compensation of Injury

The sponsor has insurance, in accordance with national regulations, covering the costs of treatment of subjects in the event of study related injuries.

19. ADMINISTRATIVE ASPECTS AND PUBLICATION

19.1 Handling and Storage of Data and Documents

The investigators must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. These documents include those required by applicable regulations, and the subjects' source documents, as described below.

Regulatory documents are those documents that individually and collectively permit evaluation of the study compliance with applicable regulations and the quality of the data produced.

These documents will be filed in an Investigator Site File (ISF) provided by the sponsor or designee. This file shall be used to facilitate and ensure filing of all relevant regulatory documents during and after the study. The investigator will be responsible for keeping the ISF updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

Source documents are original hospital records, clinical charts, screening log, subject identification lists, enrollment logs, original laboratory reports, memoranda, pharmacy dispensing records, recorded data from automated instruments, transcriptions certified after

verification as being accurate, microfiches, photographic negatives, microfilm, magnetic or electronic media, x-rays, subject's files, and records kept at pharmacy, laboratories and medico-technical departments involved in the study. The investigator must maintain source documents for each subject in the study.

All information recorded on the eCRFs must be traceable to these source documents. The investigator shall arrange for the retention of all study documents and records, including subject records, eCRFs, device inventory/accountability logs, signed ICFs and the subject identification list, after completion or discontinuation of the study for the minimum period as required per local regulation.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and the sponsor must receive written notification of this custodial change. Sites are required to inform the sponsor in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

19.2 Data Collection and electronic Case Report Forms (eCRFs)

Clinical data are collected at designated time points throughout the study. Electronic Case Report Forms (eCRFs) will be used to collect all patient data during the course of the study. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative or a regulatory authority. eCRFs must be fully completed for each subject and electronically signed by the Investigator when complete. Data will be stored in a secure, password-protected database which will be backed up periodically. Data will be reviewed using programmed and manual data checks. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Data queries will be issued to study sites for resolution. Study management reports will be generated by the sponsor (or delegate) to monitor data quality and study progress. At the end of the study, the data will be frozen and retained by the sponsor for a period of five (5) years, or as required by local regulation.

Good Clinical Practice Guidelines require that Investigators maintain information in the study subject's medical records that corroborate data collected in the eCRFs.

The Investigator or designated individual shall be responsible for recording all study data on the eCRFs provided by the sponsor. The Investigator is required to sign the eCRF on the appropriate page(s) to verify that he/she has reviewed and agrees with the recorded data.

The Investigator will allow the monitor and/or representative of the Sponsor, and any regulatory body to review and inspect the study files, subject eCRFs, subject medical records and other related study documents as required. Completed eCRFs will be verified by the appointed monitor at the investigational site at regular intervals throughout the study. Missing or unclear data will be investigated by the monitor and will be retrieved and clarified by study

personnel as necessary throughout the study. The sponsor or their authorized representative may request additional documentation from the investigator such as physician procedure notes or physician written summaries when adverse events are observed and reported.

19.3 Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

The sponsor (or delegate) is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, or terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

19.4 CIP Revisions or Amendments

During the course of the study, a revision or an amendment to the CIP may be necessary. Any revision or amendment, including justification for the modification, must be submitted to and approved by the study site’s EC and if applicable to the relevant Regulatory Authority according to local requirements prior to implementation of the amendment,

Any revisions or amendment(s) that affect the ICF require a revised, Sponsor and EC approved ICF, before changes in study procedures are implemented. These requirements should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor to preserve the safety of any subjects included in the study, as necessary.

19.5 Annual Progress Report

The sponsor/investigator will submit a summary of the progress of the study to the involved ECs once a year or according to the national / local requirements.

Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, SADEs, UADEs, DDs, protocol deviations, revisions, and amendments.

19.6 End of Study Report

The sponsor (or delegate) will notify the involved ECs and where appropriate the Regulatory Authority of the end of the study within a period of 90 days. The end of the study is defined as the last subject’s last visit.

In case the study is ended prematurely, the sponsor (or delegate) will notify the involved ECs and where appropriate the Regulatory Authorities within 15 days, including the reasons for the premature termination.

If required by the national regulations, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the involved EC and, if applicable, the Regulatory Authority within one year from the end of the study.

19.7 Public Disclosure and Publication Policy

In accordance with the sponsor's Corporate Policy on the Conduct of Human Subject Research, the sponsor requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a sponsor's study or its results. In accordance with the sponsor's Corporate Policy for the Conduct of Human Subject Research, the sponsor will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. The sponsor adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, sponsor personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.
- Sponsor involvement in the publication preparation and the sponsor Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

Publication status will be posted to the pertinent study listing on clinicaltrials.gov.

20. MONITORING

Monitoring will be performed during the study according to the study Monitoring Plan.

The Investigator/institution guarantees direct access to original source documents by sponsor personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, all reasonable attempts must be made to obtain photocopies of the original source documents for review.

It is the responsibility of the Sponsor to ensure proper monitoring of this clinical study per regulations. Trained Sponsor personnel or delegates appointed by the Sponsor may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Study Agreement, and applicable regulatory and local requirements. The Sponsor, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/ documentation) upon

request as per the ICF, Research Authorization (where applicable) and Clinical Study Agreement. The principal investigator should also be available during monitoring visits.

20.1 Monitoring Visits

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance, maintenance of study records that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff, oversight, and facilities to conduct the study safely and effectively, and review of source documents against subject eCRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify and correct non-compliance trends within the study or at a particular site.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of AEs, number and type of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study site.

21. ABBREVIATIONS AND DEFINITIONS

21.1 Abbreviations

Abbreviation	Terminology
ABI	Ankle Brachial Index
ACC/AHA	American College of Cardiology/American Heart Association
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BSC	Boston Scientific Corporation
CE	Conformité Européenne (meaning European Conformity)
CEC	Clinical Events Committee
CIN	Contrast-Induced Nephropathy
CIP	Clinical Investigational Plan
CRF	Case Report Form
CVA	Cerebrovascular Accident
DD	Device Deficiency
DES	Drug Eluting Stent
DFU	Directions For Use
DUS	Duplex Ultrasound
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDAAA	Food and Drug Administration Amendments Act
ICF	Informed Consent Form
ITT	Intent to Treat

Abbreviation	Terminology
MAE	Major Adverse Event
PI	Principal Investigator
PPA	Proximal Popliteal Artery
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
QA	Quantitative Angiography
RCC	Rutherford-Becker clinical classification
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDS	Stent Delivery System
SFA	Superficial Femoral Artery
TBI	Tibial Brachial Index
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VIVA	Vascular InterVentional Advances
WIQ	Walking Impairment Questionnaire

21.2 Definitions

Term	Definition
AMPUTATION	• Major Amputation: amputation of the lower limb at the ankle level or above. • Minor Amputation: amputation of the lower limb below the ankle level, i.e. forefoot or toes.
ANKLE-BRACHIAL INDEX (ABI)	The ratio between the systolic pressure measured at the ankle and the systolic pressure measured in the arm as follows: • Ankle: The systolic pressure will be measured in the target limb at the arteria dorsalis pedis and/or the arteria tibialis posterior. If both pressures are measured, the highest pressures will be used for the ABI calculation. • Brachial: The systolic pressure will be measured in both arms, and the highest of both pressures will be used for the ABI calculation.
ASSISTED PRIMARY PATENCY	Percentage (%) of lesions without TLR and those with TLR (not due to complete occlusion or by-pass) that reach endpoint without restenosis.
CALCIFICATION	Readily apparent densities seen within the artery wall and site of lesion as an x-ray-absorbing mass.
CEREBRO-VASCULAR ACCIDENT (CVA)	An acute symptomatic episode of neurological dysfunction attributed to a vascular cause lasting more than 24 hours or lasting 24 hours or less with a brain imaging study or autopsy showing infarction.
COMPLETE BLOOD COUNT (CBC)	A blood test used to measure several components and features of blood, including: Red Blood Cells, White Blood Cells, Hemoglobin, Hematocrit and Platelets.
COMPLICATION	An undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to perforation, occlusion, intimal flap, dissection, loss of side branch, distal embolization, hypotension, hematoma, arrhythmias, etc. Complications may or may not be related to the device(s).

Term	Definition
DEATH	All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, an unexpected death in subjects with coexisting potentially fatal non-cardiac diseases (e.g. Cancer, infection) should be classified as cardiac. All death events will be submitted to CEC and will be categorized as: Cardiac death: any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure related deaths including those related to concomitant treatment. Vascular death: death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause. Non-cardiovascular death: any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide, or trauma.
DIAMETER STENOSIS	The maximal narrowing of the target lesion relative to the reference vessel diameter.
DISSECTION-NHLBI GRADE TYPES	Type A- Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material. Type B- Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles. Type C- Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material. Type D- Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow. Type E- Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen. Type F- Filling defect accompanied by total vessel occlusion.
DISTAL EMBOLIZATION	Migration of a filling defect, or thrombus, to distally occlude the target vessel or one of its branches.

Term	Definition
EQ-5D-5L™	Descriptive system of health-related quality of life states consisting of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.
HEMATOMA	A localized swelling filled with blood resulting from a break in a blood vessel.
HEMODYNAMIC IMPROVEMENT	Improvement of ABI by ≥0.1 or to an ABI ≥ 0.90 as compared to the pre-procedure value without the need for repeat revascularization.
HYPOTENSION	Systolic blood pressure < 80 mmHg lasting more than 30 minutes or requiring intervention (e.g. pacing, IABP, intra venous vasopressors to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible.
INTIMAL FLAP	An extension of the vessel wall into the arterial lumen.
MAJOR ADVERSE EVENT (MAE)	MAE is defined as all causes of death, target limb major amputation and/or Target Lesion Revascularization (TLR)
LESION LENGTH	Measured as the distance from the proximal shoulder to the distal shoulder of the lesion, in the view that demonstrates the stenosis in its most elongated projection.
PERFORATION	Perforations are classified as follows: ***Angiographic perforation*:** perforation detected by the clinical site or Angiographic Core Laboratory at any point during the procedure. ***Clinical perforation*:** perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant hemodynamic compromise, abrupt closure, or death.

Term	Definition
PRIMARY PATENCY	Percentage (%) of lesions that reach endpoint without a hemodynamically significant stenosis on DUS and without TLR or, bypass of the target lesion.
PRIMARY SUSTAINED CLINICAL IMPROVEMENT	Endpoint determined to be a success when there is an improvement in Rutherford classification of one or more categories as compared to pre-procedure without the need for repeat TLR.
PROCEDURAL SUCCESS	Technical success with no MAEs noted within 24 hours of the index procedure.
PSEUDO-ANEURYSM	An encapsulated hematoma in communication with an artery.
REPEAT INTERVENTION (PERCUTANOUS AND/OR SURGERY)	Either repeat percutaneous transluminal angioplasty (PTA) or artery bypass surgery, performed subsequently to the subject leaving the cath lab after the index procedure.
REFERENCE VESSEL DIAMETER (RVD) OF NORMAL ARTERY SEGMENT	Angiographic measurement of the artery proximal and/or distal to the lesion intended for treatment.
RESTENOSIS	DUS systolic velocity ratio (SVR) >2.4 suggest stenosis >50%.

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td>RUTHERFORD / BECKER CLASSIFICATION</td><td>
<table>
<tr><th>Category</th><th>Clinical Description</th><th>Objective Criteria</th></tr>
<tr><td>0</td><td>Asymptomatic</td><td>Normal Treadmill /stress test</td></tr>
<tr><td>1</td><td>Mild claudication</td><td>Completes treadmill exercise; ankle pressure (AP) after exercise <50mm Hg, but >25 mm Hg less than BP</td></tr>
<tr><td>2</td><td>Moderate claudication</td><td>Between categories 1 and 3</td></tr>
<tr><td>3</td><td>Severe claudication</td><td>Cannot complete treadmill exercise and AP after exercise <50 mm Hg</td></tr>
<tr><td>4</td><td>Ischemic rest pain</td><td>Resting AP <40 mm Hg, flat or barely pulsatile ankle or metatarsal pulse volume recording (PVR); toe pressure (TP) <30 mm Hg</td></tr>
<tr><td>5</td><td>Minor tissue loss –Resting AP <60 mm Hg, ankle or nonhealing ulcer, focalmetatarsal (MT) PVR flat or gangrene with diffusebarely pulsatile; TP <40 mm Hg pedal edema</td><td></td></tr>
<tr><td>6</td><td>Major tissue loss –Same as Category 5 extending above MT level</td><td></td></tr>
</table>
</td></tr>
<tr><td>SECONDARY SUSTAINED CLINICAL IMPROVEMENT</td><td>Endpoint determined to be a success when there is an improvement in Rutherford classification of one or more categories as compared to pre-procedure including those subjects with repeat TLR.</td></tr>
<tr><td>SOURCE DATA</td><td>All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies).</td></tr>
<tr><td>SOURCE DOCUMENT</td><td>Original documents, data or records.
Examples: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.</td></tr>
</table>

Term	Definition
STENT THROMBOSIS	The occurrence of either of the following: 1. Angiographic documentation (or any other imaging modality if angiography not available) of an acute, complete occlusion of a previously successfully treated lesion and/or 2. Angiographic documentation (or any other imaging modality if angiography not available) of a flow-limiting thrombus within, or adjacent to, a previously successfully treated lesion *Acute* stent thrombosis is defined as occurring ≤24 hours following the clinical study procedure. *Subacute* stent thrombosis is defined as occurring >24 hours to ≤30 days following the clinical study procedure. *Late* stent thrombosis is defined as >30 days to 365 days following the clinical study procedure. *Very late* stent thrombosis is defined as >365 days following the clinical study procedure.
TARGET LESION REVASCULARIZATION (TLR)	Any surgical or percutaneous intervention to the target lesion(s) after the index procedure when one of the following situations is present: • A target lesion revascularization will be considered clinically-driven if it occurs within 5 mm proximal or distal to the original treatment segment with diameter stenosis ≥50% by quantitative angiography (QA) and the subject has recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible vessels.) • A target lesion revascularization for an in-lesion diameter stenosis less than 50% might also be considered a MAE by the CEC if the subject has recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible vessels.)
TARGET VESSEL	Target vessel is defined as the vessel containing the target lesion(s). If the target lesion is entirely within the right superficial femoral artery, then the target vessel is the right superficial femoral artery. If the target lesion extends from the right superficial femoral artery into the right proximal popliteal artery, then both the right superficial femoral artery and right proximal popliteal artery would be considered part of the target vessel.

Term	Definition
TARGET VESSEL REVASCULARIZATION (TVR)	Any surgical or percutaneous intervention to the target vessel(s) after the index procedure when one of the following situations is present: • A target vessel revascularization will be considered as clinically-driven if the culprit lesion stenosis is ≥50% by QA and the subject has recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible vessels.) • A target vessel revascularization for a culprit lesion diameter stenosis less than 50% might also be considered a MAE by the CEC if the subject has recurrent symptoms (≥ 1 change in Rutherford Classification or associated with decreased ABI/TBI of ≥ 20% or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible vessels.)
TRANSATLANTIC INTER-SOCIETAL CONSENSUS (TASC) LESION GUIDELINES	Type A lesion: • Single stenosis ≤ 10 cm in length. • Single occlusion ≤ 5 cm in length. Type B lesion: • Multiple lesions (stenoses or occlusions), each ≤ 5cm • Single stenosis or occlusion ≤ 15cm not involving the infra geniculate popliteal artery • Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass • Heavily calcified occlusion ≤ 5cm in length • Single popliteal stenosis Type C lesion: • Multiple stenoses or occlusions totaling > 15cm with or without heavy calcification • Recurrent stenoses or occlusions that need treatment after two endovascular interventions Type D lesion: • Chronic total occlusions of the CFA or SFA (>20cm, involving the popliteal artery) • Chronic total occlusion of the popliteal artery and proximal trifurcation vessels

Term	Definition
TECHNICAL SUCCESS	Delivery and deployment of the assigned study stent to the target lesion to achieve residual angiographic stenosis no greater than 30% assessed visually.
THROMBUS (ANGIOGRAPHIC)	Discrete, mobile intraluminal filling with defined borders with/without associated contrast straining; these are classified as either absent or present.
TOTAL OCCLUSION	Lesion with no flow; implies 100% diameter stenosis.
VASCULAR COMPLICATION	An occurrence of hematoma >5 cm, pseudoaneurysm, arteriovenous (AV) fistula, or need for vascular surgical repair.
VESSEL PATENCY	Freedom from more than 50% stenosis based on duplex ultrasound (DUS) peak systolic velocity ratio (PSVR) comparing data within the treated segment to the proximal normal arterial segment. A PSVR > 2.4 suggests >50% stenosis. All DUS readings are assessed by an independent core lab.
WALKING IMPAIRMENT QUESTIONNAIRE (WIQ)	The WIQ is a functional-assessment questionnaire that evaluates walking ability with regard to speed, distance and stair climbing ability as well as the reasons that walking ability might be limited. Range of scores is between 0% and 100% with 100% being the best and 0% being the worst score.

22. REFERENCES

1. Schillinger M, Minar E. "Claudication: Treatment options for femoropopliteal disease." *Progress in Cardiovascular Diseases* 54, no. 1 (2011): 41-46.
2. Tepe G. Schmehl J, Heller S, Wiesinger B, Claussen CD, Duda SH. "Superficial femoral artery: Current Treatment Options." *European Radiology* 16, no. 6 (June 2006): 1316-1322.
3. Erwin PA, Shishehbor MH. "Contemporary managmenet of femoral popliteal revascularization." *Intervent Cardiol Clinics* 3, no. 4 (2014): 517-530.
4. Laird JR, Katzen BT, Scheinert D, et al. "Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: Twelve month results from the RESILIENT randomized trial." *Circulation: Cardiovascular Interventions* 3, no. 3 (June 2010): 267-276.
5. Dake MD, Scheinert D, Tepe G, et al. "Nitinol stents with polymer-free paclitaxel coating for lesions in the superficial femoral and popliteal arteries above the knee: Twelve-month safety and effectivess results from the Zilver PTX single-arm clinical study." *J Endovasc Therapy* 18, no. 5 (2011): 613-23.
6. Laird JR, Katzen BT, Scheinert D, et al. "Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: Three-year follow-up from the RESILIENT randomized trial." *J Endovasc Ther* 19, no. 1 (2012): 1-9.
7. G.Ansel. "Drug-eluting stents are widely applicable: The choice of drug is the only differential factor when treating the patient." *Vascular* 18, no. Suppl 2 (June 2010): S52-53.
8. Mongiardo A, Curcio A, Spaccarotella C, Parise S, Indolfi C. "Molecular mechanisms of restenosis after percutaneous peripheral angioplasty and approach to endovascular therapy." *Current Drug Targets - Cardiovasc Haematol Disorders* 4, no. 3 (September 2004): 275-87.
9. G.Ansel. "What is the next big thing in cardiac revascularization?" *Vascular* 18, no. Suppl 2 (June 2010): S54.
10. Bosiers M, Deloose K, Keirse K, Verbist J, Peeters R. "Are drug-eluting stents the future of SFA treatment?" *J Cardiovasc Surg* 51, no. 1 (February 2010): 115-19.