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Cover Page

Statistical Analysis Plan

EMINENT

A randomized trial comparing the ELUVIA™ drug-eluting stent versus bare Metal self-expanding nitINol stEnts in the treatmeNt of superficial femoral and/or proximal popliteal arTeries

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EMINENT

S2366

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APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

Lead Biostatistician – [Insert Name and Title]	Date (dd-mon-yyyy)
Clinical Project/Trial Manager – [Insert Name and Title]	Date (dd-mon-yyyy)
Medical Director – [Insert Name and Title]	Date (dd-mon-yyyy)

Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
A 05May2021	90702621 ver AF		Initial document	Initial Release
B	90702621 ver AF	3	Update the definition for Assisted Primary Patency	Make the definition the same to protocol
B	90702621 ver AF	6.5	Remove “provided no subsequent visits occur in which PSVR<2.4 or DUS is missing, and stent segment is PATENT”	To be consistent with primary patency logic regarding DUS assessment
B	90702621 ver AF	8.3	Add within treatment groups comparison and between treatment groups comparison.	Clarify the analysis
B	90702621 ver AF	8.3.1 8.3.2.2	Add summary for subjects with re-intervention	Assessment before re-intervention needs to be summarized separately
B	90702621 ver AF	8.4.2	Update the definition for assisted primary patency, “Assisted primary patency will be defined as Primary patency using the DUS assessment among subjects without TLRs due to bypass or complete occlusion before their DUS assessment.”	Update the definition
B	90702621 ver AF	10.1	Add details for bypass of target lesion	Bypass of target lesion is not collected in AE form. It is considered as part of CD-TLR.
B	90702621 ver AF	10.2	Add details for assisted primary patency derivative	Clarify non-evaluable subjects.
C	90702621 ver AF	5.7, 6.5, 10.1, 10.2	Update the logic for primary patency and assisted patency when PSVR>2.4 and in-stent stenosis category is patent.	When PSVR>2.4 and in-stent stenosis category is patent, primary patency and assisted patency should be defined as patent.

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1 PROTOCOL SUMMARY

CIP Short title	EMINENT
CIP number	S2366
Sponsor	Boston Scientific International SA
Objective	To confirm the superior effectiveness of the ELUVIA Drug-Eluting Vascular Stent System (ELUVIA Stent) for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions up to 210 mm in length when compared against bare metal stents, and collect additional data including health economics data.
Indication(s) for Use	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.
Test Device	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.
Control Device	Commercially available stents in Europe. Permitted stents are Supera (Abbott), Lifestent (CR Bard), Everflex (Covidien/Medtronic), S.M.A.R.T. Flex (Cordis/Cardinal), S.M.A.R.T. Control (Cordis/Cardinal), Pulsar (Biotronik), COMPLETE SE (Medtronic), Misago (Terumo) or Innova (Boston Scientific) indicated for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries.
Device Sizes	**ELUVIA Stent (Test Device)** Stent Diameter (mm) / Stent Length (mm) / Recommended Vessel Diameter (mm) 6 / 40, 60, 80, 100, 120, 150 / 4.0 – 5.0 7 / 40, 60, 80, 100, 120, 150 / 5.0 – 6.0 On November 6th, 2017, Boston Scientific initiated a voluntary removal of the 150mm Eluvia™ Drug-Eluting Vascular Stent System due to elevated complaint rates for partial stent deployment. 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. **Self-Expanding Stents - Bare Nitinol (Control Devices)** Permitted stents are Supera (Abbott), Lifestent (CR Bard), Everflex (Covidien/Medtronic), S.M.A.R.T. Flex (Cordis/Cardinal), S.M.A.R.T. Control (Cordis/Cardinal), Pulsar (Biotronik), COMPLETE SE (Medtronic), Misago (Terumo) or Innova (Boston Scientific).

Study Design	A prospective, multi-center study confirming the superior effectiveness of the ELUVIA stent versus Self-Expanding Bare Nitinol Stents in the treatment of lesions 30-210 mm long located in the femoropopliteal arteries in subjects with symptoms classified as Rutherford categories 2-4. The study is a 2:1 randomized (ELUVIA vs Self-Expanding Bare Nitinol Stents), controlled, single-blind, superiority trial (RCT). Randomization will be stratified to ensure equal distribution of ELUVIA and Self-Expanding Bare Nitinol Stents in different lesion length subsets.
Primary Endpoint	<u>Primary Effectiveness Endpoint</u> The primary effectiveness endpoint assesses primary patency at 12 months post-procedure. This effectiveness endpoint is designed to demonstrate that the 12-month primary patency for the ELUVIA treatment group is superior to the Self-Expanding Bare Nitinol Stents treatment group. Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month 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
Secondary Endpoint	<u>Health-Economics</u> - Walking Improvement at 12 months assessed by change in Six Minute Hall Walk (6MHW) / treadmill test from baseline, or preceding any Target Vessel Revascularization - Walking Improvement at 12 months assessed by change in Walking Impairment Questionnaire (WIQ) from baseline - Quality of Life Improvement at 12 months assessed by change in EQ-5D-5L ™ from baseline, or preceding any Target Vessel Revascularization - Cost effectiveness of ELUVIA™ drug-eluting stent versus bare metal self-expanding nitinol stents - Rate of Primary and Secondary Sustained Clinical Improvement at 12 months as assessed by changes in Rutherford Classification from baseline - Rate of Hemodynamic Improvement at 12 months as assessed by changes in Ankle-Brachial Index (ABI) from baseline

Additional Endpoints	- Technical success - Procedural success - Major Adverse Event (MAE) rate (and individual components) at each time point, 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, 24 months and 36 months using different DUS PSVRs - Clinically-driven TLR and clinically-driven Target Vessel Revascularization (TVR) Rate at each time point - Adverse Event Rates (unanticipated, major, serious, device/procedure-related) at each time point - Survival rate at 4 years and 5 years post-procedure - Number of Stent Fractures reported at 12 months and 24 months utilizing VIVA definitions - Distribution of Rutherford Class during follow-up as compared to baseline at 1 month, 6 months, 12 months, 24 months and 36 months - Walking Improvement at 1 month, 6 months, 24 months and 36 months assessed by change in Walking Impairment Questionnaire (WIQ) from baseline - Quality of Life Improvement at 1 month, 6 months, 24 months and 36 months assessed by change in EQ-5D-5L™ from baseline - Rate of Primary and Secondary Sustained Clinical Improvement as assessed by changes in Rutherford Classification from baseline at 1 month, 6 months, 24 months and 36 months - Rate of Hemodynamic Improvement as assessed by changes in Ankle- Brachial Index (ABI) from baseline at 1 month, 6 months, 24 months and 36 months
Population	750 subjects to receive treatment with either the test device (ELUVIA, N=500 subjects) or a control device (Self-Expanding Bare Nitinol Stents, N=250 subjects). Up to 75 study centers in up to 15 European countries may enroll subjects in the study.

Study Duration	It is expected that the enrollment will take approximately 18 months. The study will be considered complete (with regard to the primary endpoint) after all subjects have completed the 12 month follow-up visit, were discontinued prior to the 12 month follow-up visit, have died, or the last 12 month follow-up visit window is closed. Subject participation will last approximately 5 years, including time required for screening. The trial will be considered complete (with regard to all follow-up) after all subjects have completed the 60 month (5 year) follow-up visit, were discontinued prior to the 60 month (5 year) follow-up visit, have died, or the last 60 month (5 year) follow-up visit window is closed. It is estimated that it will take approximately 8 years to complete this trial.
Inclusion Criteria	1. Subjects age 18 and older 2. Subject is willing and able to provide consent before any study-specific test or procedure is performed, signs the consent form, and agrees to attend all required follow-up visits 3. Chronic, symptomatic lower limb ischemia defined as Rutherford categories 2, 3 or 4 4. Stenotic, restenotic or occlusive lesion(s) located in the native SFA and/or PPA: a. Degree of stenosis ≥70% by visual angiographic assessment b. Vessel diameter ≥ 4 and ≤6 mm c. Total lesion length (or series of lesions) ≥ 30 mm and ≤ 210 mm (Note: Lesion segment(s) must be fully covered with one or two overlapping ELUVIA stent(s) or Self Expanding Bare Nitinol stent(s)) d. For occluded lesions (chronic occlusions) requiring use of re-entry device, lesion length ≤ 180 mm e. Target lesion located at least three centimeters above the inferior edge of the femur 5. Patent infrapopliteal and popliteal artery, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot with no planned intervention
Exclusion Criteria	1. Previously stented target lesion/vessel 2. Target lesion/vessel previously treated with drug-coated balloon <12 months prior to randomization/enrollment 3. Subjects who have undergone prior surgery of the SFA/PPA in the target limb to treat atherosclerotic disease 4. Use of atherectomy, laser or other debulking devices such as Rotarex in the target limb SFA/PPA during the index procedure 5. History of major amputation in the target limb

	6. Documented life expectancy less than 24 months due to other medical co- morbid condition(s) that could limit the subject's ability to participate in the clinical study, limit the subject's compliance with the follow-up requirements, or impact the scientific integrity of the clinical study 7. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated 8. Known hypersensitivity/allergy to the stent system or protocol related therapies (e.g., nitinol, paclitaxel, or structurally related compounds, polymer or individual components, and antiplatelet, anticoagulant, thrombolytic medications) 9. Platelet count <80,000 mm^3 or >600,000 mm^3 or history of bleeding diathesis 10. Concomitant renal failure with a serum creatinine >2.0 mg/dL 11. Receiving dialysis or immunosuppressant therapy 12. History of myocardial infarction (MI) or stroke/cerebrovascular accident (CVA) within 6 months prior to randomization/enrollment 13. Unstable angina pectoris at the time of randomization/enrollment 14. Pregnant, breast feeding, or plan to become pregnant in the next 5 years 15. Current participation in an investigational drug or device clinical study that has not completed the primary endpoint at the time of randomization/ enrollment or that clinically interferes with the current study endpoints (Note: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies) 16. Septicemia at the time of randomization/enrollment 17. Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention at the time of the index procedure 18. Presence of aneurysm in the target vessel 19. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to randomization/enrollment. 20. Perforated vessel as evidenced by extravasation of contrast media prior to randomization/enrollment. 21. Heavily calcified lesions. 22. As applicable by French law, subject who is a protected individual such as an incompetent adult or incarcerated person.

Method of Assigning Subjects to Treatment	Once the subject has signed the approved study Informed Consent Form (ICF), and has met all clinical inclusion and no clinical exclusion criteria, the subject will be considered eligible to be enrolled in the study. If the subject is found to meet exclusion criteria during the angiographic eligibility assessment, the subject will be considered a screen failure and should not be randomized and included in the study, nor should the subject be followed post- procedure per protocol. If the subject is found to meet the inclusion criteria during the angiographic phase of the procedure, the subject will be considered eligible to be randomized (2:1 allocation treatment versus control). Randomization will be stratified by lesion length (i.e. ≤110 mm vs. >110 mm) for each site. After the Investigator successfully crosses the target lesion with the guidewire, a randomization custom function within the eCapture electronic data capture (EDC) database will be used to assign subjects to the test or control treatment group. Subjects will be considered enrolled after they have been successfully randomized (i.e. when a treatment assignment is received by the study site).
Blinding/ **Unblinding**	The EMINENT study is a single-blind study. Subjects will be blinded to treatment assigned and treatment received. All subjects must remain blinded until completion of all 12-month follow-up visits (primary endpoint). Packaging of the test and control devices are different, therefore the investigator performing the procedure will not be blinded to the assigned treatment arm or resulting treatment. Study center personnel will be trained not to disclose the treatment assignment to the subject to minimize the potential unblinding of the subject. Site personnel conducting clinical follow-up will be blinded to a subject's treatment assignment whenever possible, and must remain blinded until completion of all 12-month follow-up visits (primary endpoint). Duplex Ultrasound Core Laboratory personnel, Angiography Core Laboratory personnel and the Clinical Events Committee (CEC) will be blinded to a subject's treatment assignment during the study. Those involved in data analysis for the Sponsor will remain blinded until the primary endpoint analysis. Instructions regarding the unblinding of a subject for a medical emergency can be found in the Unblinding guidelines.

Follow-up Schedule	All subjects will be evaluated at 6 (182 ±30 days), 12 (365 ±30 days), 24 (730 ±30 days), 36 (1095 ±30 days), 48 (1460 ±90 days) and 60 (1825 -90/+30 days) months post-procedure. Subjects will be evaluated at 1 (30 days -7 days to + 14 days) month if visit is local standard of care or if an ELUVIA stent or Self Expanding Bare Nitinol stent was not successfully implanted during the Index Procedure. • Subjects who are randomized but an ELUVIA stent or Self Expanding Bare Nitinol 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. • Assessment of the primary effectiveness endpoint and secondary health-economics endpoint will occur at the 12-month follow-up visit. • All follow-up visits through 36 months will be conducted in the office/clinic. • Telephone follow-up visit at 48 months and 60 months post-procedure, and/or medical chart review and/or publicly available records consultation, if necessary. Planned protocol-required testing includes the following: • Angiography during the index procedure, and during any subsequent revascularization procedure, to assess technical success and procedural success. • DUS at 6 months, 12 months (1 year), 24 months (2 years), and 36 months (3 years) visits to assess lesion and vessel patency. • X-rays at 12 months (1 year) and 24 months (2 years) visits to assess stent integrity will be collected if performed per standard of care. • Walking Impairment Questionnaire (WIQ) at 1 month, 6 months, 12 months (1 year), 24 months (2 years), and 36 months (3 years) visits to assess Walking Ability • EQ-5D-5L™ at 1 month, 6 months, 12 months (1 year), 24 months (2 years), and 36 months (3 years) visits to assess Quality of Life In case a subject undergoes a re-intervention of the target vessel, it is recommended to perform a walking test (6MWT or treadmill test) and QoL questionnaire (EQ-5D-5L™) prior to the Target Vessel Revascularization.
Required Medication Therapy	Investigators must prescribe concomitant anti-coagulant and anti-platelet medications consistent with current local clinical practice. Antiplatelet medication usage will be collected and reported for the duration of the trial.
Multiple Interventions Using Same Access Site	Iliac lesion(s) in both limbs may be treated during the index procedure. Iliac lesions in the target limb should be treated ***prior to*** the target SFA/PPA lesion with commercially available devices (non-drug-eluting in the target limb)

During Index Procedure	and treatment must be considered successful (i.e. residual stenosis <30% and no clinical events [embolization, perforation]) Tandem lesions in the SFA/PPA may be treated during the index procedure, provided that the tandem lesions segment is ≤ 210 mm and can be covered with one or two overlapping ELUVIA stent(s) or Self Expanding Bare Nitinol Stent(s) according to each device's Instructions for Use (IFU/DFU). (Refer to Inclusion criterion 4c.) If an additional stent is required due to complications (e.g., dissection, misplacement or under-sizing of the target lesion), the additional stent(s) placed should be of the same type used to treat the target lesion.
Statistical Methods	<u>Primary Effectiveness Statistical Hypothesis</u> The primary effectiveness hypothesis to be tested is that the 12-month primary patency in subjects treated with ELUVIA is superior to subjects treated with Self Expanding Bare Nitinol Stents at one-sided significance level of 2.5%. <u>Primary Effectiveness Statistical Test Method</u> The Chi-Square Test will be used to assess the hypothesis of superiority in proportions: H_0: Pt - Pc ≤ 0 H_1: Pt - Pc > 0 (superior) where Pt and Pc are the 12-month primary patency for the ELUVIA (test) and Self Expanding Bare Nitinol Stents (control) groups, respectively. <u>Secondary Health-Economics endpoint</u> No formal tests of hypotheses are proposed for the secondary endpoint. Statistical comparisons may be performed for exploratory purposes.

Sample Size Parameters	The primary effectiveness endpoint drives the overall sample size. <u>Primary Effectiveness Endpoint</u> • Power ≥ 85% • One-sided significance level (alpha) = 2.5% • To demonstrate 10%* treatment effect in effectiveness: • Expected ELUVIA 12-month primary patency = 85% • Expected Self Expanding Bare Nitinol Stents 12-month primary patency = 75% • Allocation (ELUVIA vs. Self-Expanding Bare Nitinol Stents) = 2:1 • Attrition rate in 12 months ≤ 16% • A minimum of 630 evaluable subjects are required at 12 months (ideally 420 ELUVIA, 210 Self Expanding Bare Nitinol Stents) • Approximately 750 subjects are planned to be randomized in a 2:1 fashion at enrollment *The 10% treatment effect represents 7% observed advance. Assuming a 12-month primary patency of 75.2% (158/210) is observed for Self Expanding Bare Nitinol Stents, a minimum of 82.1% (345/420) for ELUVIA will be required to claim superiority.

2 ASSESSMENT SCHEDULE

Procedure/Assessment	Pre-procedure[3]	During Index Procedure	Pre-Discharge	1 MFU[10] (30 -7 days to + 14 days)	6 MFU (182±30 days)	12 MFU (365±30 days)	24 MFU (730±30 days)	36 MFU (1095±30 days)	48MFU [11] (1460 ± 90 days)	60 MFU [11] (1825 -90 / +30 days)	Prior to TVR
Informed Consent[1]	X										
In/exclusion criteria	X	X									
Demographics & Medical History	X										
Laboratory[2]	X										
Pregnancy test[3]	X										
ABI	X			X[4]	X	X	X	X			
RCC (Rutherford-Becker clinical classification)	X			X	X	X	X	X			
WIQ	X			X	X	X	X	X			
EQ-5D-5L	X			X	X	X	X	X			X[9]
6MHW or treadmill[8]	X					X[8]					X[9]
Angiogram[5]		X									
Randomization		X									
DUS[5]					X	X	X	X			
X-Ray[6]						X[6]	X[6]				
Health Economics				X	X	X	X	X			
Medication	X	X	X	X	X	X	X	X			X
Adverse Events[7]		X	X	X	X	X	X	X	X	X	X

1. Subject's consent may be obtained outside the 30 day window leading up to the procedure however, subject's consent and informed consent form must be signed prior to any study-specific tests or procedures
2. Serum Creatinine and Platelet Count to be measured
3. Performed within 30 days of procedure, except informed consent and except urine or blood pregnancy test required for females of childbearing potential performed within 7 days of procedure
4. ABI measurement may be collected immediately post-procedure through 1 Month Follow-up window (Day 0 – 44)
5. Angiograms and DUS 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 36-month follow-up timeframe, or has a documented occluded stent.
6. X-ray only to be performed if per standard of care. If X-ray is done, images to be sent to the core lab for analysis.
7. Reporting required through the end of study for Major Adverse Events, UADEs, and (S)ADEs/Device Deficiencies.
8. Pre-procedure and at 12MFU, either 6MWT or treadmill can be performed, whatever is standard of care.
9. In case a subject undergoes a re-intervention of the target vessel, it is recommended to perform a walking test (6MWT or treadmill test) and QoL questionnaire (EQ-5D-5L™) prior to the TVR
10. The 1 month visit is only required if the visit is local standard of care or if an ELUVIA stent or Self Expanding Bare Nitinol stent was not successfully implanted during the index procedure.
11. The 48 month and 60 month visit will be conducted via telephone and/or medical chart review and/or publicly available records consultation.

3 ABBREVIATIONS AND DEFINITIONS

Abbreviation	Terminology
ABI	Ankle Brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific Corporation
CEC	Clinical Events Committee
CRF	Case Report Form
CVA	Cerebrovascular Accident
DES	Drug Eluting Stent
DUS	Duplex Ultrasound
EDC	Electronic Data Capture
FDA(AA)	Food and Drug Administration Amendments Act
ICF	Informed Consent Form
ITT	Intent to Treat
MAE	Major Adverse Event
PAS	Post Approval Study (reports)
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

Abbreviation	Terminology
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
VIVA	Vascular InterVentional Advances
WIQ	Walking Impairment Questionnaire
6MHW	Six Minute Hall Walk

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.

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.
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.
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.
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.

Term	Definition
MAE	MAE is defined as all causes of death, target limb major amputation and/or Target Lesion Revascularization (TLR)
Primary patency	Percentage (%) of subjects whose lesions reach endpoint without a hemodynamically significant stenosis on DUS and without clinically driven 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.
Repeat intervention (percutaneous 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 peak 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 – nonhealing ulcer, focal gangrene with diffuse pedal edema</td><td>Resting AP <60 mm Hg, ankle or metatarsal (MT) PVR flat or barely pulsatile; TP <40 mm Hg</td></tr>
<tr><td>6</td><td>Major tissue loss – extending above TM level</td><td>Same as Category 5</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>
</table>

Term	Definition
Stent fracture	A break in one or more places of the stent. The following definitions will be used to determine the type and extent of stent fracture (to be assessed by the x-ray core laboratory):[3] • Grade 0: No Strut fractures • Grade I: single strut fracture • Grade II: multiple strut fractures • Grade III: stent fracture(s) with preserved alignment of the components • Grade IV: stent fracture(s) with mal-alignment of the components • Grade V: Stent fracture(s) in a trans-axial spiral configuration
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	A target lesion is identified as a clinical study lesion intended to be treated with a test or control device during the index procedure.

Term	Definition
Target lesion revascularization (TLR)	Any surgical or percutaneous intervention to the target lesion(s) after the index procedure: • A target lesion revascularization will be considered clinically-driven by the CEC 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 (toe brachial index) of ≥ 0.2 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 ≥ 0.2 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.
Target vessel revascularization (TVR)	Any surgical or percutaneous intervention to the target vessel(s) after the index procedure: • A target vessel revascularization will be considered as clinically-driven by the CEC 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 ≥ 0.2 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 ≥ 0.2 or ≥ 0.15 in the treated segment. TBI allowed in cases of incompressible 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.
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.

4 INTRODUCTION

The Statistical Analysis Plan (SAP) documents the planned analyses to be consistent with the objectives of the EMINENT protocol for the randomized controlled trial (RCT) comparing ELUVA with bare metal stents in the treatment of Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions. The specified analyses may be provided in reports to competent authorities and/or for scientific presentations and/or manuscripts.

For the RCT a total of 750 subjects are planned to be randomized at a ratio of 2:1 to treatment with ELUVIA of bare metal nitinol stents. The primary endpoint analysis will be performed once all subjects have completed 12 months follow up. Further analysis will be performed on the additional endpoints as later follow up data is collected.

Details of additional planned analyses and reports generated from the study data (including ELUVIA annual reports and post approval study (PAS) reports for submission to FDA, as well as periodic safety reports) will be included in the appendix to this document.

5 GENERAL STATISTICAL METHODS

All statistical analyses will be performed by the Biostatistic vendor, iQVIA, using SAS 9.4 (Copyright © SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

All data management activities will be documented in the Data Management Plan.

For continuous and ordinal variables, descriptive statistics will include mean, standard deviation, number of observations, minimum and maximum. Specific variables may also include additional statistics such as median, interquartile range (IQR) and confidence intervals. For binary or categorical variables, the descriptive statistics will include percentage, numerator, denominator and number of missing observations if applicable. Some variables may include confidence intervals where specified.

5.1 Analysis Sets

The intention-to-treat (i.e. as-randomized) analysis set will be the primary analysis set for assessing superiority of ELUVIA to bare metal stents, as well as for all secondary and additional endpoints. The per-protocol analysis will also be presented for the primary endpoint (if not identical to the intention-to-treat analysis set). The As-treated analysis set will be assessed in safety analyses and where specified herein.

5.1.1 Intention-To-Treat (ITT)

All subjects who sign the informed consent form (ICF), are randomized in the RCT will be included in the ITT analysis set, regardless of whether the subjects receive the assigned treatment.

5.1.2 Per-Protocol (PP)

For the PP analysis, only randomized subjects who meet the eligibility criteria and receive the assigned treatment will be included in the PP analysis set. Subjects who do not receive the randomized device(s) or who have protocol deviations that impact the primary analysis will be excluded from the PP analysis set. Protocol deviations that could impact the primary effectiveness endpoint and require subjects to be excluded from the Per-Protocol population will be documented.

5.1.3 As-Treated (AT)

For the AT analysis, subjects who receive either ELUVIA or bare metal stents at procedure will be included in the AT analysis set according to the treatment they actually received (even if it was not the treatment they were randomized to). Subjects who do not receive ELUVIA or study permitted bare metal stents will be excluded from the AT analysis set.

5.2 Randomization Scheme

Randomization will be determined at the point of treatment. Randomization to treatment will be stratified by study site and lesion length (stratification by lesion length only after protocol Revision 2. A computer generated list of random treatment allocations (i.e., a randomization schedule) will be used to assign subjects to treatments in a 2:1 ratio of

Test Group to Control Group by lesion length (i.e. ≤110 mm vs. >110 mm) for each study site. This list will be specific to the subject's site. Random permuted blocks of varying sizes will be employed to ensure approximate balance of treatment allocation within each stratum.

5.3 Control of Systematic Error/Bias

Selection of subjects will be made from the Investigators' general or professional referral population. All subjects meeting the inclusion/exclusion criteria and who have signed the protocol-specific ICF will be eligible for enrollment in the trial. Consecutively eligible subjects should be enrolled into the trial to minimize selection bias. Study subjects will be randomly assigned to a treatment group within the investigational site at the point of treatment. In determining subject eligibility for the study, the investigator's assessment of imaging will be used. However, the Angiographic Core Laboratory will independently analyze the angiograms and the data obtained from the core laboratory will be used for analyses. An independent CEC composed of medical experts will adjudicate safety assessments, as defined in the CEC Charter.

5.4 Number of Subjects per Investigative Site

Study sites will not be allowed to randomize more than 10% (N=75) of the total number of randomized subjects without prior approval from the sponsor. No study site will be allowed to enroll more than 20% (N=150) of the total number of randomized subjects.

5.5 Analysis Timepoints

5.5.1 Visit Windows

For all endpoints assessed at specific timepoints (primary patency, walking improvement, QoL, Rutherford classification, hemodynamic improvement, rates of TLR and TVR, rate of stent fracture and rate of adverse events), only assessments which occurred within the protocol defined window for the timepoint will be included in the analysis, unless otherwise specified. Time to event (Kaplan-Meier) analyses will include events reported within the upper limit of the visit window (e.g. up to day 395 for the 12 month assessment). The visit day is defined as *Date of assessment - Date of randomization.*

Analysis timepoint	Nominal visit day	Lower window	Upper window
1 month post procedure	30	23	37
6 months post procedure	182	152	212
12 months post procedure	365	335	395
24 months post procedure	730	700	760
36 months post procedure	1095	1065	1125
48 months post procedure (telephone call/chart review)	1460	1370	1550
60 months post procedure (telephone call/chart review)	1825	1735	1855

5.5.2 Interim Analyses

There are no planned interim analyses for this study.

5.5.3 Data Snapshot and Report Timings

A data snapshot will be taken after all patients reach the 12 months follow-up visit (or experience a clinically driven TLR, or are withdrawn from the study). The Primary Endpoint Report will present data for all endpoints at 1 month, 6 months and 12 months (if appropriate). The final analysis will be performed after all patients have completed the five-year survival follow up. Regular snapshots of data will be taken as patients reach time points for scheduled reports (i.e. PAS reports to FDA and CTSR reports).

5.6 Handling of Missing Data, Drop Outs and Protocol Deviations

5.6.1 Missing Data

For all analyses, unless otherwise specified, the number of subjects with valid data will be presented in the tables (for categorical data the number of subjects with missing data will be displayed), as well as the total number in the analysis set at that timepoint. The total which was used as the denominator in any percentage calculations will be identified where these numbers differ.

5.6.2 Protocol Deviations

Protocol deviations will be summarized by category, and details will be provided of those leading to a decision to exclude from the Per-Protocol analysis set.

5.7 Changes to Planned Analyses

All planned analyses described in the protocol will be performed. Additional analyses on long term mortality will also be performed on the study data as described in section 8.6. Kaplan-Meier (time to event) analyses will be performed on the primary endpoint (Time to Loss of Patency), and on Time to MAEs/TLR/clinically driven TLR.

In protocol version 2 the nine months follow up visit was removed from the protocol, however data was collected for some patients prior to the revision. This data will not be analyzed, however it will be reported in listings on completion of the study.

Primary patency is defined as a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 in the absence of clinically-driven TLR or bypass of the target lesion. In the rare situation where PSVR>2.4 and in-stent stenosis category equal to 'Patent' with correlating factors indicating a <50% stenosis, the subjects will be considered as a success for primary patency. This additional logic will be applied for the future analysis.

5.7.1 Impact of COVID-19 Pandemic

The impact of the pandemic on hospitals means that follow up visits for study patients were missed or delayed. The primary endpoint excludes subjects with missing data, therefore considerably fewer subjects than originally planned may be included in the primary endpoint analysis. This is a randomized study, and it is not expected that the

patency rates within each arm will be impacted due to COVID-19 infection, so it is not anticipated that results will be biased, assuming patients miss visits at the same rate between treatment arms. The decreased number of evaluable patients may, however, lead to diminished power to statistically demonstrate the anticipated treatment effect, even if it is truly observed. The observed power for the total number of patients included in the primary endpoint analysis will be calculated based on a) the original assumed treatment effect, and b) the observed treatment effect. Once the extent of missing data is known, further approaches may be considered (for example, but not limited to: further sensitivity analyses, imputation of missing data and inclusion of data from later study assessments).

The planned sensitivity analysis (tipping point analysis) imputes all combinations of values for subjects with missing data and explores which point the conclusion of the trial might change. From this it will be possible to deduce the outcome of the trial, had all the patients been included and had the rates been the same as those observed from the available data.

To account for the impact of the anticipated volume of missing data due to the pandemic, results from the sensitivity analysis will be considered alongside the main primary effectiveness results when determining the overall outcome of the trial.

6 PRIMARY ENDPOINT ANALYSIS

The sample size for the study was determined to provide adequate power for the primary effectiveness endpoint based on the statistical hypothesis.

Whilst results will be presented and compared between treatment groups for other endpoints, the study was designed for formal hypothesis testing on the primary effectiveness endpoint only. The primary effectiveness analysis will be performed on the ITT analysis set and Per-Protocol analysis set.

6.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint assesses primary patency at 12 months post-procedure. This effectiveness endpoint is designed to demonstrate that the 12-month primary patency for the ELUVIA treatment group is superior to the Self-Expanding Bare Nitinol Stents treatment group.

6.1.1 Definition of Primary Patency

Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month follow-up visit in the absence of clinically-driven TLR or bypass of the target lesion.

- Vessel patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment.
- A PSVR >2.4 suggests >50% stenosis.
- The stented segment will be assessed for patency as a single segment regardless of the number of tandem lesions within the stented segment.

- All DUS will be assessed by an independent core laboratory.
- Clinically-driven TLR is determined by the CEC and is defined as a re-intervention within 5 mm proximal or distal to the original treatment segment for > 50% angiographic diameter stenosis in the presence of recurrent symptoms (≥ 1 change in Rutherford class) or associated with decreased ABI/TBI of ≥ 0.2 or ≥ 0.15 in the treated segment. Tibial Brachial Index (TBI) allowed in cases of incompressible vessels.

6.1.2 Effectiveness Hypotheses

The primary effectiveness hypothesis to be tested is that the 12-month primary patency in the Test Group is superior to the Control Group at one-sided significance level of 2.5%.

The null hypothesis (H0) states that there is no treatment effect between the Test Device vs. the Control Device as opposed to the alternative hypothesis (H1) which states that there is a treatment effect. The hypotheses inequalities are shown below:

H_0: $P_t - P_c \leq 0$
H_1: $P_t - P_c > 0$ (superior)

Pt and Pc are the 12-month primary patency proportions for the Test Device and Control Device, respectively.

6.1.3 Sample Size

The primary effectiveness endpoint drives the overall sample size. Approximately 750 subjects are planned to be enrolled. The sample size justification is based on the following assumptions:

- Expected ELUVIA (Test Device) 12-month primary patency proportion = 85%
- Expected Self Expanding Bare Nitinol Stents (Control Device) 12-month primary patency proportion = 75%
- Test significance level (α) = 2.5% (1-sided)
- Power ($1-\beta$) ≥ 85%
- Expected rate of attrition in 12 months = 16%

With a sample size allocation (Test vs. Control) of 2 to 1, a minimum of 630 evaluable subjects in total (420 in the Test Group and 210 in Control Group) will be required at 12 months to provide at least 85% power under a one-sided 2.5% significance level.

The trial will demonstrate 10% treatment effect which represents 7% observed advance. Assuming a 12-month primary patency of 75.2% (158/210) is observed for Self Expanding Bare Nitinol Stents, a minimum of 82.1% (345/420) for ELUVIA will be required to claim superiority.

Taking into account the assumed attrition rate of 16%, this amounts to the enrollment of approximately 750 subjects (500 in the Test Group and 250 in Control Group).

6.1.4 Statistical Methods

The primary effectiveness hypothesis will be tested using a Chi-square test. The null hypothesis will be rejected and ELUVIA will be demonstrated to be superior to bare metal stents, if primary patency for ELUVIA is greater than for bare metal stents and if $p<0.05$. The 95% CI around the proportion difference (risk difference) will also be presented.

The primary effectiveness analysis will incorporate data from DUS assessments made at the 12-month study visit and clinically driven TLR events reported prior to and at that visit. Only subjects with adequate follow up and a valid DUS assessment will be included in the denominator for the analysis, unless they experienced clinically driven TLR prior to that, in which case they will be considered not to be patent (i.e. a failure on the binary endpoint). Subjects will be considered to have adequate follow up if they have not died or discontinued from the study and the number of days since their index procedure is greater than the lower limit of the visit window (see Section 5.5.1). Subjects with DUS assessments later than the upper limit for the visit window will be included in the analysis if their assessment shows them to be patent (including assessments confirming patency made at the scheduled 24 or 36 months visit).

6.2 Sensitivity Analysis for Missing Primary Endpoint Data

A sensitivity analysis for the primary effectiveness endpoint assessment will be conducted to assess the impact of missing data on the robustness of the results. The sensitivity analysis will be performed on the ITT analysis set using the same data snapshot as the primary endpoint analysis (i.e. incorporating all available primary endpoint data). A "tipping point" analysis will be performed to assess the impact of missing data. Within each treatment group, all scenarios will be imputed (i.e. considering 0, 1, 2… up to all of the missing values as patent). All combinations of these scenarios for the ELUVIA and bare metal stent groups will be analyzed in the same way as the primary effectiveness endpoint. Pairs of scenarios (where the number of patients imputed as patent changes by 1 in either group) which led to outcomes on either side of the $p=0.05$ threshold will be presented. A plot will be displayed showing the proportion of missing entries imputed as successes per treatment arm that correspond to the $p=0.05$ threshold.

6.3 Justification of Pooling

The poolability across sites will be assessed by means of a logistic regression with site and treatment as factors in the model. If the p-value of poolability test in the logistic regression model for the primary endpoint is > 0.15, the treatment effect will be presented for overall across all sites. If the p-value is ≤ 0.15, the treatment effect will be presented by site as well as over all sites.

Sites that have fewer than 6 individual subjects enrolled, or two per treatment arm will not be included in the regression.

6.4 Multivariable Analyses

Univariable and multivariable analyses will be performed to assess the effect of potential predictors for the primary effectiveness endpoint in a logistic regression model. Each of

the factors identified below will first be assessed in a univariate model. Any factors from the univariate models that are significant ($p<0.05$) will be included in the multivariate model, which will be refined by a process of backwards elimination, whereby factors are eliminated one by one if they are not significant (using the same threshold). The study is not primarily designed to identify significant risk factors and all results should be interpreted in accordance with clinical meaning.

The following baseline covariates will be entered in the regression model, in addition to treatment group: race, gender, age group, diabetic status, chronic total occlusion, (moderate/severe) calcification, vessel diameter (continuous), lesion length (≤110 mm vs. >110 mm), stent diameter (categorical) and stent length (categorical).

6.5 Kaplan-Meier for Primary Patency Failure

A Kaplan-Meier analysis will be performed on time to loss of primary patency. This analysis will be performed using the 12 months data snapshot for the primary endpoint report and will be repeated using the final data snapshot at the final analysis. Events occurring before the upper limit of the visit window will be included in the analysis. Time to patency failure is defined at the time after index procedure at which the first of these occurs:

- Clinically driven TLR or bypass
- DUS measurement with PSVR>2.4 during the visit window (in-stent stenosis category is not patent)
- DUS PSVR is missing and stent segment is 50-99% or OCCLUDED during the visit window

Subjects not experiencing any of the above will be censored at the date of their last study visit or at the upper limit of the visit window (i.e. day 396 for the 12 month visit).

The estimated proportion of subjects that are event free at 1, 6 and 12 months for the primary endpoint report, and also at 24 and 36 months for the final report, will be displayed for each treatment group with standard error and 95% confidence intervals. Time to event will be compared between treatment groups using a log-rank test.

6.6 Subgroup Analyses

Primary endpoint will be summarized and treatment groups compared in subgroups identified by the following categories:

- Race
- Gender (male vs. female)
- Age (≥ 65 and <65)
- Diabetic status (medically-treated, defined as those treated with oral agents or insulin vs. non-diabetic)
- Lesion length (≤110 mm vs. >110 mm)

- Vessel diameter (≤ 5mm vs < 5mm)
- Stent use (single vs multiple)
- Other significant predictors identified by regression models

No formal tests of hypotheses are proposed for subgroups and therefore alpha-adjustment for multiple comparisons is not required. Where groups are scarcely represented (i.e. <~10% of the study population) they may be combined or those analyses omitted.

7 SAFETY ANALYSES

Safety analyses will be performed on the As Treated analysis set.

7.1 Adverse Event Coding

AEs will be coded using MedDRA and presented according to system order class (SOC) and preferred term (PT) in tables. CEC reported events that were not coded will be reported separately.

7.2 Missing Event Dates Considerations

All event rates will be calculated relative to the date of procedure, and only treatment emergent (i.e. post-procedure) events will be reported.

When event dates are missing or partially missing, in the first instance, efforts will be made to obtain the dates by liaison with safety and/or data management representatives to query sites for missing data. Failing this, missing and partial missing dates may be handled as using the worst case scenario as follows:

Partial Date Description	Action Taken
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

7.3 Safety Endpoints

The safety endpoints for the study are:

- Major Adverse Event (MAE) rate (and individual components) at each time point, defined as all causes of death, target limb major amputation and/or Target Lesion Revascularization (TLR)

- Adverse Event Rates (unanticipated, major, serious, device/procedure-related) at each time point

7.3.1 Rate of MAEs (and CEC Adjudicated Events)

Rate of MAEs will be reported for 1 month, 6 months and 12 months in the Primary Endpoint Report, and over all timepoints in the final report.

The protocol-defined MAEs include:

- all causes of death
- target limb major amputation
- TLR

In addition, the rates of all CEC adjudicated events will be presented, including MAEs as defined above, as well as

- TVR
- Stent thrombosis

Minor target limb amputations will also be included. Deaths will be categorized as cardiac, vascular and non-cardiovascular. TLR and TVR will be categorized as clinically driven and not clinically driven.

For both tables, the denominator will otherwise be based on number of subjects who reach the protocol-defined lower window (i.e. adequate follow-up days, see section 5.5.1) and/or subjects who experience an event. The numerator will be based on number of subjects who experience events within the protocol-defined upper window. Subjects with events that occur beyond the upper window will be counted at the next time point. Total CEC adjudicated events, total MAEs, and totals for each of the individual events defined above will be displayed. Rates will be compared between treatment arms using chi square tests.

Note: Previous studies with ELUVIA stents adopted a definition of MAE that only included deaths occurring up to 1 month post procedure. The protocol for EMINENT does not specify that only deaths occurring in the first month should be included therefore that definition will not be adopted here.

7.3.2 Analysis of Site-Reported Serious and Non-Serious Adverse Events

The number of site reported events within the first 12 months follow up will be presented in the Primary Endpoint report. The final report will summarize events for the entire duration of the study. The denominator for this table will include all patients in the As Treated population, regardless of whether they reached the protocol defined lower window for adequate follow up (i.e. patients who died, were lost to follow up, or missed the study visit are included in the denominator)

The number of patients reported by the site to have experienced events classified as unanticipated, major, serious and procedure/device related (defined as related to index procedure or related to implanted stent, respectively) will be summarized at each

timepoint regardless of whether or not they are ultimately adjudicated to be (or lead to) a MAE. A table of serious and non-serious events by MedDRA SOC and PT will be presented. Number of events as well as number of subjects will be presented. Listings will be provided of non-MedDRA coded events and unanticipated adverse device events.

7.4 Other Safety Analyses

7.4.1 Kaplan-Meier for Time to MAE/TLR

A Kaplan Meier analysis will be performed on time to any MAE and time to TLR and clinically driven TLR. These analyses will be performed using the 12 months data snapshot for the primary endpoint report and will be repeated using the final data snapshot at the final analysis. All events occurring prior to the upper limit of the visit window will be included in the analysis. Time to event will be the time after index procedure at which the first event occurs. Subjects not experiencing events will be censored at the date of their last clinic visit, or at the upper limit of the visit window (i.e. day 396 for the 12 month analysis).

The estimated proportion of subjects that are event free at 1, 6 and 12 months for the primary endpoint report, and also at 24 and 36 months for the final report, will be displayed for each treatment group with standard error and 95% confidence intervals. Time to event will be compared between treatment groups using a log rank test.

8 ADDITIONAL ANALYSES

Results will be presented and compared between treatment groups for baseline characteristics, and for secondary and additional endpoints. Results up to the 12 month follow up will be displayed in the Primary Endpoint report, and all timepoints will be displayed in the final report.

Statistical comparisons (including p-values) may be performed where specified for exploratory purposes only. Continuous secondary endpoints will be compared by means of t-tests; rates or incidences will be compared between ELUVIA and control arm by means of Chi-square test (or exact tests if the assumptions are not met for Chi- square). No formal inferences are planned on the secondary endpoints and additional endpoints and therefore alpha-adjustments for multiple comparisons will not be used.

8.1 Patient Disposition

The number of subjects enrolled per site in each treatment arm will be presented. A disposition table will be presented at each of the study timepoints (1, 6, 12, 24, 36, 48 and 60 months), displaying deaths/withdrawals/reasons for withdrawal/ /eligibility for follow up.

8.2 Baseline Data and Procedure Details

Baseline data from study site and core lab, post treatment measurements from core lab, and ultrasound measurements from core lab (at timepoints from 6 months onwards) will be presented in the primary endpoint report and final report for the ITT and As Treated analysis sets.

Procedural data including details of stent placement will be presented in the Primary Endpoint Report and the Final Report for the As Treated analysis set.

Data will be presented by treatment group. For core lab angiography results, treatment groups will be compared by t-tests (continuous data) and Chi-square tests (categorical data), or exact tests if the assumptions for Chi-square tests are not met.

8.2.1 Medications

Patients receiving antiplatelet medications (prior to study, at discharge and at each timepoint) and which medications received will be summarized.

Stent fractures will be listed for ELUVIA stents only at the 12 month time point (in the Primary Endpoint report) and at 12 and 24 months in the final report.

8.3 Secondary Endpoints

The secondary endpoints as follows will be assessed for the ITT analysis set. Results will be presented for 1 month, 6 months and 12 months in the Primary Endpoint Report, and at all timepoints in the final report, with the exception of the six-minute walk test, which is only assessed at the 12 months time point.

- Walking Improvement at 12 months assessed by change in Six Minute Hall Walk (6MHW) / treadmill test from baseline, or change from baseline to preceding any Target Vessel Revascularization
- Walking Improvement at 12 months assessed by change in Walking Impairment Questionnaire (WIQ) from baseline
- Quality of Life Improvement at 12 months assessed by change in EQ-5D-5L™ from baseline, or change from baseline to preceding any Target Vessel Revascularization
- Rate of Primary and Secondary Sustained Clinical Improvement at 12 months as assessed by changes in Rutherford Classification from baseline
- Rate of Hemodynamic Improvement at 12 months as assessed by changes in Ankle-Brachial Index (ABI) from baseline

8.3.1 Walking Improvement (6MHW)

Improvement in the 6MHW test will be measured either at the 12-month visit, or prior to reintervention (TVR). Results will be presented separately for measurements made prior to reintervention.

The change from baseline to 12 months in each group will be compared using paired t-test. The average difference in total walk time, total distance walked and total distance walked per minute will be compared between treatment groups using a two-sample t-test at 12 months.

For subjects who had target vessel revascularization before or at 12-month visit, the measurement prior to re-intervention and the change from baseline to re-intervention will be summarized separately.

8.3.2 Patient Reported Outcomes (PRO)

Two PRO tools (i.e. WIQ and EQ-5D^{TM}) will be used to assess each subject at baseline (pre-procedure), 1 month, 6 months, 12 months, 24 months, 36 months, and 60 months. The absolute scores and changes (e.g. improvement over time from baseline will be presented descriptively. The p-values for changes within treatment groups and between treatment groups will be presented.

8.3.2.1 Walking Impairment Questionnaire (WIQ)

The questionnaire characterizes subjects' self-reported degree of difficulty in walking and contains 4 sections of questions: 1) a Peripheral Arterial Disease specific question and a list of differential diagnoses, 2) Walking Distance (7 items), 3) Walking Speed (4 items), and 4) Stair Climbing (3 items).

The responses are ranked on a scale of 0 to 4, (0=unable to do, 4=no difficulty). Subjects are instructed to give the response "unable" when the limitation was due to claudication pain.

Symptoms that could limit walking performance are also characterized in question 1, and the degree of difficulty in walking caused by a symptom is graded. The PAD specific question evaluates pain, aching or cramps in the calf or buttock (characteristic of intermittent claudication). Only the responses to this question will be reported as a percentage (where a score of zero is 0%, 1 is 25%, 2 is 50%, 3 is 75% and 4 is 100%).

The questions relating to differential diagnosis (pain, stiffness or aching of joints (arthritis); weakness in the legs (neuromuscular dysfunction); and chest pain, dyspnea, or palpitations (typical of cardiopulmonary disorders) enable assessment of comorbid disorders that could limit ambulation in addition to claudication. Responses to these questions will be presented in listings only.

A weighted-average score will be constructed for questions 2-4. For example, for Walking Distance, if a subject responds with a 3 (slight difficulty) for the first 5 items, a 2 (some difficulty) for walking 900 feet, and a 0 (unable to do) for walking 1,500 feet, the summary score for this subject will be calculated as:

The raw score: 3*20 + 3*50 + 3*150 + 3*300 + 3*600 + 2*900 + 0*1,500 = 5,160

The Maximal score for Walking Distance: 4*(20 +50 +150 +300 +600 +900 +1,500) = 14,080

The summary score: 5,160/14,080 = 36.65%

The summary scores for Walking Speed (the maximal score of 46) and Stair Climbing (the maximal score of 288) are similarly derived.

The percentage scores will be summarized for each of the four questions, and number and percentage of patients showing improvement compared to baseline at each timepoint will be presented and compared between treatment arms using Chi-square test

8.3.2.2 Euro-Qol (EQ-5D™)

The EQ-5D™ is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

The EQ-5D™ descriptive system is designed to best describe current health self-reported by subject. It consists of 5 five questions (EQ-5D-5L), each with 5 possible responses, and a visual analogue scale (EQ VAS) assessing overall health scale (0 to 100, worst to best).

Scoring of EQ-5D-5L

There are 5 questions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The answer provided will be assigned a number based on the response selected, where 1 is the most positive response and 5 is the worst as indicated below.

MOBILITY
I have no problems in walking about (1)
I have slight problems in walking about (2)
I have moderate problems in walking about (3)
I have severe problems in walking about (4)
I am unable to walk about (5)
SELF-CARE
I have no problems washing or dressing myself (1)
I have slight problems washing or dressing myself (2)
I have moderate problems washing or dressing myself (3)
I have severe problems washing or dressing myself (4)
I am unable to wash or dress myself (5)
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
I have no problems doing my usual activities (1)
I have slight problems doing my usual activities (2)
I have moderate problems doing my usual activities (3)
I have severe problems doing my usual activities (4)
I am unable to do my usual activities (5)
PAIN / DISCOMFORT
I have no pain or discomfort (1)
I have slight pain or discomfort (2)
I have moderate pain or discomfort (3)
I have severe pain or discomfort (4)
I have extreme pain or discomfort (5)
ANXIETY / DEPRESSION
I am not anxious or depressed (1)
I am slightly anxious or depressed (2)
I am moderately anxious or depressed (3)
I am severely anxious or depressed (4)

I am extremely anxious or depressed (5)

The responses to the five questions will be summarised at each timepoint, and the number of patients with improved response for each question compared to baseline will be presented.

The responses to all five questions will be summarised as a five-digit code, representing the five responses in turn, e.g if the responses are

Mobility: 1
Self-care: 2
Usual activities: 2
Pain/discomfort: 4
Anxiety/depression: 2

The five-digit code for this patient would be 12242.

The code can be converted into a single index value, dependent on the country where the data was collected. A list of index values for each code for each country can be downloaded from the EuroQol website:

https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

The list will be downloaded from the website at the time of analysis and the date of download documented. The list will be imported into SAS and the index value will be assigned by matching the five-digit code and country. If any of the responses are missing, it is not possible to assign a five-digit code, and therefore not possible to assign an index.

For each of the five questions, the number and percentage reporting each response will be presented across all timepoints, as well as the number and percentage improving for each category at each timepoint.

The index values will be presented as mean, standard deviations, N (not missing), minimum and maximum across all timepoints.

Paired t-tests will be used to determine whether significant improvements have been observed compared to baseline within treatment arms, and average improvement between treatment arms will be compared by two-sample t-test.

Scoring of the EQ-VAS

EQ-VAS scores will be presented as N (not missing) mean, standard deviations, median, IQR, minimum and maximum.

Paired t-tests will be used to determine whether significant improvements have been observed compared to baseline within treatment arms, and average improvement between treatment arms will be compared by two-sample t-test.

For subjects who had target vessel revascularization, the measurement prior to re-intervention and the change from baseline to re-intervention will be summarized separately.

8.3.3 Primary and Secondary Sustained Clinical Improvements, Defined as Improvement in Rutherford Class During Follow-up as Compared to Baseline at 1 month, 6 months, 12 months, 24 months and 36 months

The rates of primary and secondary sustained clinical improvements will be assessed as changes in Rutherford classification from baseline at 1 month, 6 months, 12 months, 24 months, and 60 months.

Primary sustained clinical improvement is defined as an improvement in Rutherford classification of one or more categories as compared to baseline without the need for repeat TLR. Hence a prior TLR may suggest "not an improvement" regardless of upgrade in Rutherford classification.

Secondary sustained clinical improvement is defined as an improvement in Rutherford classification of one or more categories as compared to baseline including those subjects with repeat TLR.

Clinical deterioration is defined as downgrade in Rutherford classification of one or more categories as compared to baseline.

The rate of primary and secondary improvement will be compared between treatment groups (Chi-square test).

8.3.4 Hemodynamic Improvement

The rate of hemodynamic improvement is to assess the changes in ABI from baseline at 1 month, 6 months, 12 months, 24 months, and 36 months. The definition of improvement is to observe either the ABI measurement ≥ 0.9 or the change from baseline ≥ 0.1 without the need for repeat TLR. Therefore a prior TLR may suggest "not an improvement" regardless of ABI measurements.

There are two scenarios for hemodynamic improvement shown below.

Subject #1's baseline ABI= 0.95 and 12-month ABI= 1.0. The subject #1 shows 12-month improvement due to 12-month observed ABI= 1.0.

Subject #2's baseline ABI= 0.6 and 12-month ABI= 0.8. The subject shows 12-month improvement due to the ABI increase of 0.2 (i.e. 0.8 – 0.6) regardless of 12-month ABI measurement of 0.8 (i.e. <0.1).

Note that the ABI deterioration is defined as observing 0.1 or more in ABI decrease from baseline.

The rate of hemodynamic improvement will be compared between treatment groups (Chi-square test).

8.3.5 Cost Effectiveness

Cost effectiveness of ELUVIA™ drug-eluting stent versus bare metal self- expanding nitinol stents will be analysed by the Market Access group on the basis of the results for the above, as well as summaries of the following.

- Number of physician visits for PAD
- Number of amputations of target limb
- Number of TVRs
- Number of days in rehabilitation related to PAF
- Number of days in hospital related to PAD

These results will be included in the primary endpoint reports and final report.

Readmission rates and summaries of number of days in hospital for AEs, for device related AEs, and for TVR/TLR will be presented by country in the primary endpoint report and the final report.

8.4 Additional Endpoints

8.4.1 Technical and Procedural Successes

Technical success is defined as delivery and deployment of the assigned study stent to the target lesion to achieve residual angiographic stenosis no greater than 30% assessed visually.

Procedural success is defined as technical success with no MAEs noted within 24 hours of the index procedure.

The number of successes will be compared between treatment groups using a Chi-square test (or exact test if the assumptions are not met).

8.4.2 Primary Patency and Assisted Primary Patency at 6 months, 12 months, 24 months and 36 months Using Different DUS PSVRs

Primary patency will be assessed at each of the time points in the same way as described in the primary effectiveness analysis. Assisted primary patency will be defined as primary patency using the DUS assessment among subjects without TLRs due to bypass or complete occlusion before their DUS assessment.

Primary and assisted primary patency will be assessed using a PSVR cut off of both 2.4 and 2.0.

8.4.3 Survival Rate at 4 and 5 Years

The survival rate at 4 and 5 years post procedure will be calculated based on survival status data available at that time.

A Kaplan Meier analysis will be conducted using the date of reported death. Patients without reported deaths will be censored at their last known date of contact. Median survival and estimated survival proportion at 1, 2, 3, 4 and 5 years will be presented, with

95% confidence intervals. Survival will be compared between treatment groups using the log rank test. This will be included in the final report.

8.4.4 Number of Stent Fractures Reported at 12 months and 24 months Utilizing VIVA Definitions

Details of stent fractures occurring at the 12 and 24 month timepoints will be listed.

8.5 Listings

Listings of all CRF data will be produced.

8.6 Other Analyses Not Specified in the Protocol

8.6.1 Time-To-Event Kaplan-Meier Analysis

Kaplan Meier analyses of time to loss of primary patency, time to MAE and time to TLR were not specified in the protocol but will be performed for the primary endpoint report (i.e. when all patients reach 12 months follow up), and again at completion of the study for inclusion in the final report.

9 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation.

10 PROGRAMING CONSIDERATION

All statistical programming tasks including blinding and unblinding analyses will be performed by the independent CRO (iQVIA). The BSC statistician(s) remain blinded until the independent CRO unblinds the primary results.

10.1 Derivation for Primary Patency

The primary patency is based on PSVR measurement derived from the core laboratory data provided by Vascular Ultrasound Core Lab (i.e. VASCORE), clinically driven TLR determined by CEC form, and bypass surgery of target lesion which is not documented separately, and considered as a part of clinically driven TLR. For example, a subject's 12-month primary patency is derived as patent (i.e. "YES") only if:

- VASCORE form: a subject's 12-month DUS assessment is done and PSVR ≤ 2.4 or 'Patent' determined by the in-stent stenosis category when PSVR is 'NA' or 'UNK' or when PSVR>2.4 and in-stent stenosis category shows 'Patent'; and
- CEC form: no clinically-driven TLR prior to 12-month DUS visit. Note that if there is one clinically-driven TLR and the event date is later than (>) 12-month DUS visit, the subject's primary patency will remain "YES".

10.2 Derivation for Assisted Primary Patency

The assisted primary patency is based on PSVR measurement derived from VASCORE form only. A subject's 12-month assisted primary patency is derived as "YES" only if the subject's 12-month DUS visit is within 12-month window and PSVR ≤ 2.4 or 'Patent'

determined by the in-stent stenosis category when PSVR is 'NA' or 'UNK' or when PSVR>2.4 and in-stent stenosis category shows 'Patent'. If subjects had CD-TLR due to bypass or complete occlusion prior to 12-month DUS, these subjects will be treated as non-evaluable subjects even if they had diagnostic DUS at 12-month. However, if CD-TLR is after 12-month DUS, 12-month DUS will be used to assess 12-month assisted primary patency. If DUS is missing at 12-month, the next available DUS will used to impute 12-month assisted primary patency if it shows patency and there is no CD-TLR due to bypass or complete occlusion prior to it. Assisted primary patency at other visits will be derived similarly.

CD-TLR due to bypass is derived using CD-TLR corresponding AE form (TVR). If type of revascularization is surgery, then it is CD-TLR due to bypass; CD-TLR due to complete occlusion is derived using CD-TLR corresponding additional angiography form from Re-Intervention Core Lab. If re-stenosis in stent (MLD re-angio/ stent MLD index) is 100%, it is CD-TLR due to complete occlusion.

10.3 Example SAS Code for Primary Endpoint Analysis

The following is example code to calculate the risk different in primary patency between groups, with 95% confidence interval, and to conduct the chi square test for determination of whether the primary effectiveness endpoint is met.

```
proc freq data=data;
     table trt*patent / sparse out=counts CL alpha=0.05
riskdiff;
run;

proc freq data=data noprint;
   tables trt*patent / chisq out=_epval2 sparse outexpect
exact;
  output out=test  chisq exact;
  run;
```

where `trt` is a variable indicating treatment arm and `patent` is a binary variable indicating primary patency for each subject at 12 months.

Table of Contents (TOC) for tables, listings, and figures for primary endpoint analysis