Evaluation of Safety and Effectiveness of the BioMimics 3D™ Stent System in the Femoropopliteal Arteries of Patients with Symptomatic Peripheral Arterial Disease

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Investigator's Signature Page

STUDY TITLE: MIMICS-2: Evaluation of the Safety and Effectiveness of the BioMimics 3D™ Stent System in the Femoropopliteal Arteries of Patients with Symptomatic Peripheral Arterial Disease

PROTOCOL NUMBER & ISSUE: CID 100 Issue 09

STUDY CENTER:

_____

(Print name of study center)

I, the undersigned, have read and understand the Protocol specified above and agree with its content. I agree to perform and conduct the Study as described in the Protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the Study as described in the Protocol. I will provide copies of this Protocol and all pertinent information to the Study personnel under my supervision and my hospital Institutional Review Board/Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the BioMimics 3D investigational device and the conduct of the Study according to Good Clinical Practice (GCP), Declaration of Helsinki, 21 CFR Parts 50, 54, 56 and 812, ISO 14155:2011, and any local regulations.

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SITE PI – Print Name

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SITE PI – Signature

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DATE

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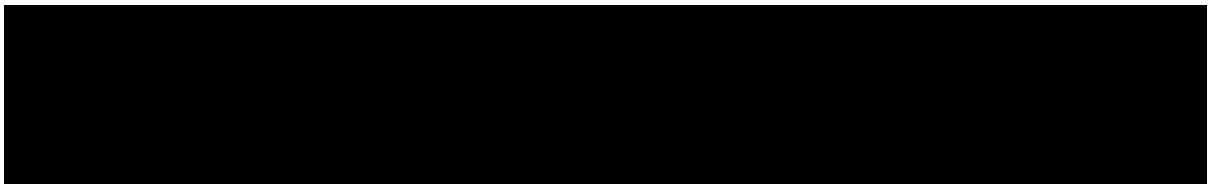

PROTOCOL SUMMARY

Study Title:	MIMICS-2: Evaluation of Safety and Effectiveness of the BioMimics 3D™ Stent System in the Femoropopliteal Arteries of Patients with Symptomatic Peripheral Arterial Disease
Study Objective:	To demonstrate that the BioMimics 3D Stent System meets the performance goals defined by VIVA Physicians, Inc. for the safety and effectiveness of Nitinol stents used in the treatment of symptomatic disease of the femoropopliteal artery.
Study Device:	BioMimics 3D™ Stent System
Intended Use:	The BioMimics 3D stent is intended to improve luminal diameter in the treatment of symptomatic de-novo, obstructive or occlusive lesions up to 140 mm in length in native femoropopliteal arteries with reference vessel diameters ranging from 4.0 – 6.0 mm
Study Design:	Prospective, single-arm, multicenter clinical trial
Device Regulatory Status:	United States Class III investigational device Europe CE Mark approval (Class IIb) Japan Class III investigational device BioMimics 3D Stent System has been designed and is manufactured by Veryan Medical Limited under the control of Veryan's Quality Management System. Veryan is ISO 13485 certified.
Estimated Enrollment:	280 subjects. Up to 40% (112 subjects) of total study population may be enrolled outside the United States No site may enroll more than 35 subjects.
Subject Population:	Subjects with symptomatic atherosclerotic disease of the femoropopliteal artery who comply with all study eligibility criteria.
Clinical Sites:	Up to 40 centers in the United States. Up to 13 centers in Japan and Europe.
Study Follow-Up:	After the index procedure on Day 0, subjects will be evaluated within 30 days, then at Months 12, 24 and 36.
Study Duration:	First subject enrolled: June, 2015 Last subject enrolled: October, 2016 Last subject completes Month 12 Visit: December, 2017 Last subject completes Month 24 Visit: December, 2018 Long-term surveillance completed (Month 36): December, 2019
Primary Outcome Measures:	Primary safety endpoint: A composite of major adverse events (MAE) comprising death, any major amputation performed on the target limb or clinically-driven target lesion revascularization (TLR) through 30 days.

	Primary effectiveness endpoint: Primary stent patency rate at 12 months. Patency is defined as no significant reduction in luminal diameter (i.e. < 50% diameter stenosis) since the index procedure. Luminal diameter is assessed by core lab using angiography or duplex ultrasound imaging. Loss of primary stent patency is deemed when peak systolic velocity ratio (PSVR) is >2.0, or where angiography reveals >50% diameter stenosis, or where the subject undergoes clinically-driven TLR. When both imaging modalities are available, angiography takes precedence. [redacted]
Secondary Outcome Measures:	1. Contribution of individual MAE rates for death, major amputation performed on the target limb and clinically-driven target lesion revascularization to the overall MAE rate at 30 days. 2. Long-term safety assessment – overall MAE rate at Month 12 and contribution of individual event rates to the overall MAE. 3. Overall rate and incidence of type of serious adverse events from Day 0 through completion of Study follow-up at Month 36. 4. Technical success reported by the core lab as the percentage of treated lesions in which a final result of ≤50% residual diameter stenosis (in-stent) was achieved at index procedure. 5. Primary stent patency rate: determined at Months-12 and 24 using values of: PSVR >2.0; >2.4; >2.5; and >3.5, each to indicate loss of patency on duplex ultrasound or where angiography reveals >50% diameter stenosis or where the subject undergoes clinically-driven TLR. When both imaging modalities are available, angiography takes precedence. [2] 6. Clinical outcome: comparison of Rutherford Clinical Category measured at Baseline, Day 30, Months 12 and 24. Worsening of Rutherford Clinical Category is defined as an increase by one or more categories compared to Baseline or unexpected major amputation of the target limb. 7. Clinical outcome: comparison of Six-Minute Walk Test measured at Baseline, Day 30, Months 12 and 24 (subgroup of US investigational sites only).

[redacted]

	8. Functional outcome: comparison of the ankle brachial index (ABI) measurement at Baseline, within 30 days after index procedure, then at Months 12 and 24. 9. Functional outcome: comparison of the Walking Impairment Questionnaire at Baseline, within 30 days after index procedure, then at Months 12 and 24. 10. Stent integrity measured as freedom from stent fracture, defined as clear interruption of a stent strut observed in a minimum of two projections, determined by core lab examination of X-rays taken with the leg in extension at 12, 24 and 36 Months.
[redacted]	[redacted]
Inclusion Criteria:	1. Subject is male or female, with age >18 and ≤85 years at date of enrollment. 2. Subject or authorized representative provides written informed consent before any study-specific investigations or procedures. 3. Subject is willing to undergo all follow-up assessments according to the specified schedule over 36 months. 4. Subject is a suitable candidate for angiography and endovascular intervention and, if required, is eligible for standard surgical repair. 5. Subject has symptomatic peripheral arterial disease (PAD) of the lower extremities requiring intervention to relieve de novo obstruction or occlusion of the native femoropopliteal artery. 6. Subject has PAD classified as Rutherford clinical category 2, 3 or 4. 7. Subject has documented PAD by either (i) a resting ankle-brachial index (ABI) of ≤0.90 (or ≤0.75 after exercise of the target limb). Resting toe brachial index (TBI) is performed only if unable to reliably assess ABI. TBI must be <0.70; or (ii) Normal ABI with angiographic or ultrasound evidence of ≥60% diameter stenosis.
Angiographic Inclusion Criteria:	8. Subject has single or multiple stenotic or occlusive lesions within the native femoropopliteal artery (“target lesions”) that can be crossed with a guidewire and fully dilated. (Note: multiple target lesions must be treated as a single lesion.) 9. Single or multiple target lesions must be covered by a single stent or two overlapping stents. In the case of tandem lesions, the gap between lesions must be ≤ 3 cm. 10. Target lesion(s) eligible for treatment under the Protocol are at least 1 cm distal to the origin of the deep femoral artery and at least 3 cm above the bottom of the femur. 11. Target lesion(s) reference vessel diameter is between 4.0 mm and 6.0 mm by operator’s visual estimate. 12. Single or multiple target lesions measure ≥40 mm to ≤140 mm in overall length, with ≥60% diameter stenosis by operator’s visual estimate. 13. Subject has a patent popliteal artery (no stenosis ≥50%) distal to the treated segment. 14. Subject has at least one patent infrapopliteal vessel (<50% stenosis) with run-off to the ankle.

Exclusion Criteria:	1. Subject is unable or is unwilling to comply with the procedural requirements of the study Protocol or will have difficulty in complying with the requirements for attending follow-up visits. 2. Subject has a comorbidity that in the investigator's opinion would limit life expectancy to less than 36 months. 3. Subject has iliac stent in target limb that has required re-intervention within 12 months prior to index. 4. Subject has any planned major surgical procedure (including any amputation of the target limb) within 30 days after the index procedure for this Study. 5. Subject has a target vessel that has been treated with any type of surgical or endovascular procedure prior to enrollment. 6. Subject has a target vessel that has been treated with bypass surgery. 7. Subject has PAD classified as Rutherford clinical category 0, 1, 5 or 6. 8. Subject has known or suspected active systemic infection at the time of enrollment. 9. Subject has a known coagulopathy or has bleeding diatheses, thrombocytopenia with platelet count less than 100,000/microliter or INR >1.8. 10. Subject has a stroke diagnosis within 3 months prior to enrollment. 11. Subject has a history of unstable angina or myocardial infarction within 60 days prior to enrollment. 12. Subject has a contraindication to antiplatelet, anticoagulant, or thrombolytic therapies. 13. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-medicated. 14. Subject has known allergy to titanium, nickel or tantalum. 15. Subject has received thrombolysis within 72 hours prior to the index procedure. 16. Subject has acute or chronic renal disease (e.g., as measured by a serum creatinine of >2.5 mg/dL or >220 umol/L), or on peritoneal or hemodialysis. 17. Subject requiring coronary intervention within 7 days prior to enrollment. 18. Subject is pregnant or breast-feeding. 19. Subject is participating in another research study involving an investigational product (pharmaceutical, biologic, or medical device). 20. Subject has other medical, social or psychological problems that, in the opinion of the investigator, preclude them from receiving this treatment, and the procedures and evaluations pre- and post-treatment.
Angiographic Exclusion Criteria:	21. Subject has significant disease or obstruction (≥50%) of the inflow tract that has not been successfully treated at the time of the index procedure (success measured as ≤30% residual stenosis, without complication). 22. Subject has a lesion in the contralateral limb requiring intervention during index procedure or within next 30 days.

	23. Subject has no patent (≥50% stenosis) outflow vessel providing run-off to the ankle. 24. There is a lack of full expansion in the predilatation balloon. 25. Target lesion(s) requires percutaneous interventional treatment, beyond standard balloon angioplasty alone, prior to placement of the study stent. 26. Evidence of aneurysm or acute thrombus in target vessel.
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1.0 INTRODUCTION AND BACKGROUND

1.1 Introduction

Veryan intends to conduct a prospective, single arm, multicenter trial (MIMICS-2) to demonstrate the safety and effectiveness of Veryan's BioMimics 3D Stent System. The BioMimics 3D self-expanding Nitinol stent is intended to improve luminal diameter in the treatment of symptomatic de-novo obstructive or occlusive lesions in native femoropopliteal arteries with reference vessel diameters ranging from 4.0 – 6.0 mm. Up to 280 subjects will be enrolled into MIMICS-2 and treated with the BioMimics 3D Stent System. Safety and effectiveness outcomes in the MIMICS-2 study will be compared to established performance goals defined by VIVA Physicians, Inc. for the clinical evaluation of safety and effectiveness of Nitinol stents used in the treatment of symptomatic disease of the femoropopliteal artery.

1.2 Literature Summary

Atherosclerosis is a chronic vascular disease that can manifest itself in the coronary, neurovascular and peripheral vascular beds with end organ and distal extremity vascular impact. Specifically, peripheral arterial disease (PAD) is a common manifestation of atherosclerosis and is a chronic occlusive arterial disease caused by plaque buildup in the arterial lumen that leads to diminished blood flow. The rising prevalence of PAD with increasing age, and within a population increasingly at risk from obesity and diabetes, is a major international health care issue with substantial economic ramifications. In the United States alone, Medicare-funded, in-patient costs for PAD have been estimated to total $4 billion annually [1]. A recent estimate concluded that the global prevalence of PAD presently exceeds a quarter of a billion and that this number grew by more than 20% in the period 2000 to 2010 [2]. Patients with PAD have an increased risk of myocardial infarction, stroke, and death [2]. Major risk factors for the development of PAD include family history, age, hypertension, cigarette smoking, diabetes, and dyslipidemia; the greatest risk factors being diabetes and smoking [2]. The treatment of PAD is initially directed at a combination of lifestyle or behavioral modification and medical management to hopefully slow the disease and symptom progression. When these methods fail to provide symptomatic relief, revascularization may be achieved through endovascular or surgical approach [2].

Anatomically, 70% of PAD lesions are present in the femoropopliteal and tibial arteries with more than 50% of all PAD interventions involving the superficial femoral and popliteal arteries [3]. Femoropopliteal disease is characterized by long, diffuse obstructive or occlusive lesions that create a unique slow-flow and high resistance environment [3]. The treatment of the femoropopliteal arteries using endovascular treatments has gained popularity with patients and physicians alike due to these procedures being less invasive, and potentially with fewer complications, than the surgical options [4], [5].

The immediate treatment goal for patients with PAD is relief of symptoms arising from intermittent claudication. The ultimate long-term goal is preservation of tissue or limb salvage. When lifestyle or behavioral modification and conservative medical therapy fail, surgical intervention may be a consideration for these patients [6]. An open surgical procedure continues to be a standard treatment modality but is associated with longer recovery, greater costs and potential complications (i.e., general surgical and anesthesia-related complications, thrombosis of the bypass graft, infection, etc.). As endovascular interventional techniques have advanced in both treatment success and long-term durability, endovascular therapy is increasingly the preferred option to treat patients with PAD whose symptoms are refractory to optimal exercise programs and medical therapy [3].

Percutaneous transluminal angioplasty (PTA) is one of the simplest endovascular methods to treat PAD, but the acute success of the technique is often dependent on the lesion morphology [7]. The effectiveness of PTA in the femoropopliteal artery may be compromised by calcium deposition in the arterial wall that may contribute to elastic recoil and suboptimal outcome [8]. Acute failure of PTA in

moderate length lesions (<10 cm) was reported as 40% in the Resilient trial [9] and at 50% in the Zilver PTX trial [10]. A number of non-randomized studies have demonstrated that PTA can yield acceptable long term results in focal lesions [11]–[13]; however, success of the technique in longer lesions is hampered by a high incidence of restenosis [14], [15]. A recent study which reviewed the safety and effectiveness of PTA for the treatment of femoropopliteal lesions up to 15 cm in length (mean 8.7 cm) revealed a 12-month primary patency rate of 33% [16].

Nitinol stents were developed as an adjunctive endovascular therapy to provide scaffolding to the arterial wall, thus preventing elastic recoil, and treating intimal injuries post-angioplasty [17]. Endovascular stenting is frequently used to recanalize the peripheral vessels [18]–[20]. However, despite improvements in stent design, restenosis is a limiting factor as a result of intimal hyperplasia following stent placement [21]. The mechanism for the development of restenosis is multi-factorial but may include vessel injury during angioplasty, stent implantation, sub-optimal flow conditions and mechanical factors. Recently, the STELLA study reported a 12 month fracture rate of 17.7% in patients with long lesions (mean lesion length 220mm) [22]. Iida *et al.* reported a fracture rate of 14% and noted that stent fracture was more prevalent in longer lesions [23]. In a review by Rits *et al.* the highest stent fracture rate reported was 65%, with the highest occurrence in the superficial femoral artery (SFA) [24]. Ansel *et al.* reported a fracture rate of 31% at 12 months in the Nitinol stent study arm and observed that fractures predominantly occurred in longer lesions (>150mm) [25]. Allie *et al.* reported that stent fractures were linked to restenosis in 77% of stent fractures [26]. Scheinert *et al.* reported that over two-thirds of cases of stent fracture were associated with restenosis or reocclusion [27]. These data have underscored the need for a new approach to the design of stents for the peripheral vessels in general and the SFA in particular.

Given that the SFA and popliteal arteries are under continuous mobility during knee flexion the resultant mechanical forces on the vessel include compression, flexion, extension, torsion and pulsatile distension (see Figure 1). Stents deployed in these vessels are also subjected to these forces [28]. The suitability of a stent for the femoropopliteal artery may therefore depend on its ability to shorten in a controlled manner, without inducing strains which lead to fatigue fracture [29]. The inability of long and /or multiple straight stent segments to shorten or "take up the slack" during motion, leads to large strains, kinking and fatigue fractures [28], [30]. In addition, if the stent is unable to shorten, it may create biomechanical incompatibilities leading to acute and chronic injury to adjacent vessel segments subjected to substantial deformation where knee flexion may induce acute vascular angulation (kinking) [30]–[32]. A stent which can shorten naturally in order to reduce focal deformation and provide longitudinal flexibility may therefore provide a favorable solution for recanalization of the SFA.

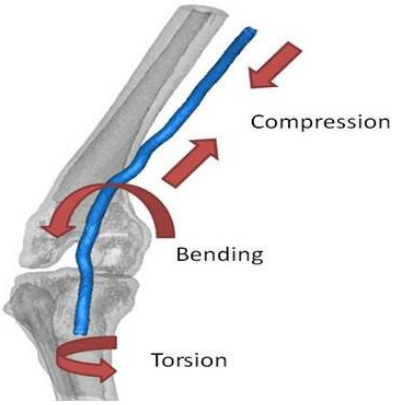

Figure 1: Forces on the femoropopliteal artery during lower limb movement

Local hemodynamics are strongly influenced by vessel morphology and the vascular endothelium is constantly exposed, and highly sensitive to, the prevailing wall shear stress. Shear stress of physiological arterial magnitudes (>1.5 pascals) is reported to produce an atheroprotective endothelial phenotype that renders the endothelium less susceptible to pathogenic stimuli [33]. Deleterious flow modifications resulting in low wall-shear stress in an artery (< 0.4 Pa) are both pro-atherogenic and a focus for intimal hyperplasia [34], [35]. It has been shown that endovascular stenting not only physically damages the endothelium but also disturbs blood flow, creating regions of low wall shear stress leading to endothelial activation and initiation and progression of intimal hyperplasia [36]. The stimulation of endothelial cells by arterial wall shear stress therefore plays a central role in the restenotic process. Any tendency for a stent in the distal part of the long SFA to

straighten natural vessel geometry in this longest of arteries may jeopardize protective swirling blood flow imparted by the helically curved common iliac arteries [*data on file*]. In summary, the design hypothesis for Veryan's BioMimics 3D stent is that by imparting 3D geometry to the vessel it will help to maintain normal physiological swirling flow and normal wall shear stress levels and, in conjunction with improved biomechanical performance, there is the prospect of improved outcomes.

1.3 Novel Technology

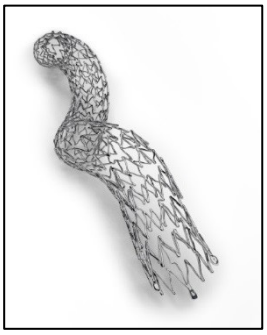

Figure 2: BioMimics 3D Stent

The BioMimics 3D stent (see Figure 2) is a permanently implanted, self-expanding Nitinol stent designed to maintain luminal patency in the endovascular treatment of patients with symptomatic peripheral arterial disease of the superficial femoral and/or popliteal (femoropopliteal) arteries.

The design of the BioMimics 3D stent is built on the principles underlying the latest generation of Nitinol stent technology for use in the femoropopliteal artery: an appropriate level of mechanical radial support and plaque coverage; good flexibility; durability against fracture; clear visualization and delivery accuracy.

1.4 Report of Prior Investigations

Refer to the Investigator's Brochure for a detailed description of the pre-clinical (bench, animal and cadaver) testing performed with the BioMimics 3D Stent and Stent Delivery System and full details on

the Mimics clinical study. [redacted]

[redacted]

2.0 DEVICE INDICATION FOR USE AND DEVICE DESCRIPTION

2.1 Intended Use

The BioMimics 3D stent is intended to improve luminal diameter in the treatment of symptomatic de-novo obstructive or occlusive lesions up to 140 mm in length in native femoropopliteal arteries with reference vessel diameters ranging from 4.0 – 6.0 mm.

2.2 Device Description

The BioMimics 3D Stent System consists of:

- A Nitinol stent with a three dimensional (3D) helical profile in a range of lengths and diameters
- An over-the-wire (OTW) stent delivery system.

Stent

The BioMimics 3D stent is a peripheral self-expanding nickel-titanium alloy (Nitinol) stent with 3D helical centerline geometry. The stent is laser cut from a straight Nitinol tube and 3D helical geometry is stored in the Nitinol shape memory. Three tantalum radiopaque markers are located at both ends of the stent.

Stent Delivery System

The BioMimics 3D stent is mounted on a 6F over-the-wire stent delivery system (SDS) for use with a 0.035" guidewire. The SDS is shown in Figure 7 and consists of the inner shaft (8) and outer braided stainless steel sheath (9) secured together via the Tuohy Borst valve (3). The operating length of the SDS, comprising proximal (5), middle (6) and distal (7) sections, is 1128 ±8 mm.

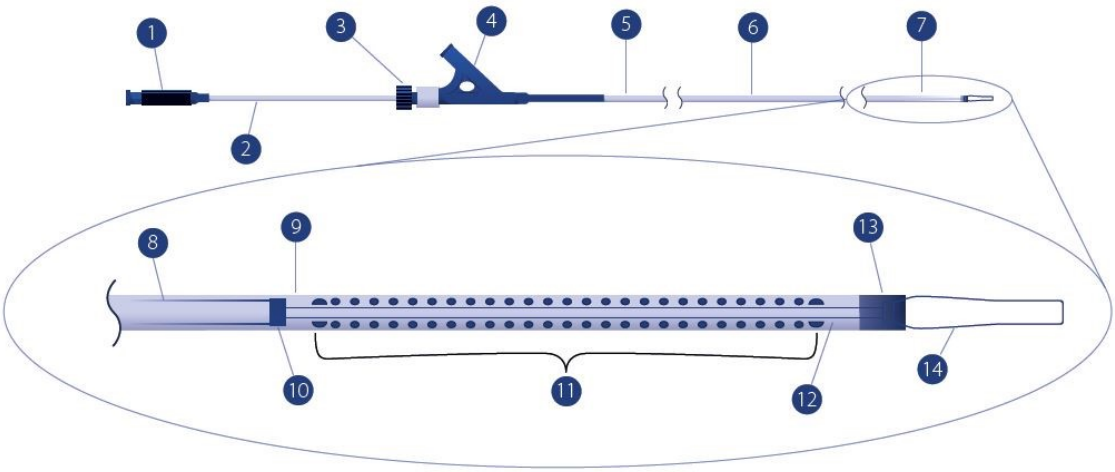

Figure 7: BioMimics 3D stent delivery system components

1.	Luer Hub	8.	Inner Shaft
2.	Support Shaft	9.	Outer Braided Sheath
3.	Tuohy Borst Valve	10.	Inner Shaft Marker
4.	Bifurcated Luer	11.	BioMimics 3D Stent
5.	Proximal Section	12.	Inner Liner
6.	Middle Section	13.	Outer Sheath Marker
7.	Distal Section	14.	SDS Tip

The inner shaft consists of a luer hub (1), bonded to a stainless steel support shaft (2) and inner shaft (8) assembly. A radiopaque inner shaft marker band (10) is located at the assembly distal end. An inner liner (12) runs the length of the device and is the lumen through which the guidewire passes. The radiopaque tip (14) is attached to the inner liner distal end.

The outer sheath consists of a Tuohy Borst valve (3), bonded to the bifurcated luer (4) which attaches to the outer braided sheath (9). A radiopaque marker (13) is located at the distal end of the outer sheath.

The stent (11) is crimped and loaded into the space between the inner shaft and the outer sheath at the distal end of the SDS immediately proximal to the radiopaque tip.

Table 6 provides information on the dimensions of the BioMimics 3D stent and stent delivery system.

Table 6: BioMimics 3D stent and delivery system size matrix

Unconstrained Stent Internal Diameter (mm)	Stent Length (mm)	Minimum-Maximum Reference Vessel Diameter (mm)	Stent Delivery System Operating Length (cm)	Stent Delivery System Outer Diameter	Minimum Sheath Inner Diameter	Guide Wire Compatibility
5	60, 80, 100, 125, 150	[redacted] 4.0	112.8	0.079”	0.088”	0.035”
6		4.0 - 5.0				
7		5.0 - 6.0				

[redacted]

2.3 Device Preparation and Deployment Procedure

The BioMimics 3D Stent will be prepared and deployed as described in the "Instructions for Use" that accompanies each device. The standard of care for subject preparation and follow-up, including medication and vascular access, will be followed according to the requirements of this Protocol and hospital / institutional standards of care.

3.0 INVESTIGATIONAL PLAN

3.1 Study Objective

The Primary Objective is to demonstrate that the BioMimics 3D Stent System meets the performance goals defined by VIVA Physicians, Inc. for the safety and effectiveness of Nitinol stents used in the treatment of symptomatic disease of the femoropopliteal artery.

3.1.1 Study Design

Prospective, single arm, multi-center trial in which study subjects will receive treatment with Veryan's BioMimics 3D Stent System.

3.1.2 Enrollment

A total of 280 subjects will be enrolled into the MIMICS-2 Study to provide 230 subjects for evaluation at 12 months. This study will be conducted in up to 40 centers in the US and up to 13 centers in Europe and Japan. Up to 40% of total study population may be enrolled outside the US. A minimum of 30 evaluable subjects is required in Japan for the 12 month assessment time point. No site may enroll more than 35 subjects.

3.1.3 Study Population

Subjects with symptomatic atherosclerotic disease of the femoropopliteal artery that comply with all study eligibility criteria.

3.2 Study Duration and Follow-Up

The Study commenced enrollment in June, 2015. Enrollment was closed in October, 2016. Study subjects will be required to return for clinic visits post-procedure at Day 30 (± 7 days), Month 12 (365 days ± 30 days), and Month 24 (730 days ± 60 days). A final study visit at Month 36 (1095 days ± 60 days) is required as well; however, this visit may be completed either as a clinic visit or telephone visit. The 36 month visit is expected to be in the post-market surveillance phase of the study. All subjects will be followed with duplex ultrasound and X-ray evaluation according to the Schedule in Table 7. The last follow-up visit is expected to be completed by December, 2019, at the last subject's 36 month follow-up visit.

4.0 STUDY ENDPOINTS AND SUBJECT POPULATION

4.1 Primary Outcome Measures

4.1.1 Primary safety endpoint:

The primary outcome measure for safety in the MIMICS-2 Study is a composite of major adverse events (MAE) comprising death, any major amputation performed on the index limb or CDTLR through 30 days. The outcome will be compared to the safety performance goal of 88% for bare Nitinol stenting as defined by VIVA Physicians.

4.1.2 Primary effectiveness endpoint:

The primary outcome measure for effectiveness in the MIMICS-2 Study is primary stent patency rate at 12 months. Patency is defined as no significant reduction in luminal diameter (i.e., < 50% diameter stenosis) since the index procedure. Luminal diameter is the value determined by the independent core lab. Loss of primary stent patency is deemed when PSVR >2.0, or where angiography reveals >50% diameter stenosis, or where the subject undergoes CDTLR. When both imaging modalities are available, angiography takes precedence.

[redacted]

[redacted]

4.2 Secondary Outcome Measures

1. Contribution of individual MAE rates for death, major amputation performed on the target limb and CDTLR to the overall MAE rate at 30 days.
2. Long-term safety assessment – overall MAE rate at Month 12 and contribution of individual event rates to the overall MAE.
3. Overall rate and incidence of type of serious adverse events from Day 0 through completion of Study follow-up at Month 36.
4. Technical success reported by the core lab as the percentage of treated lesions in which a final result of ≤50% residual diameter stenosis (in-stent) was achieved at index procedure.
5. Primary stent patency rate: determined at Months 12 and 24 using values of: PSVR >2.0; >2.4; >2.5; and >3.5, each to indicate loss of patency on duplex ultrasound or where angiography reveals >50% diameter stenosis or where the subject undergoes CDTLR. When both imaging modalities are available, angiography takes precedence. [6]
6. Clinical outcome: comparison of Rutherford Clinical Category measured at Baseline, Day 30, Months 12 and 24. Worsening of Rutherford Clinical Category is defined as an increase by one or more categories compared to Baseline or unexpected major amputation of the target limb.
7. Clinical outcome: comparison of Six-Minute Walk Test measured at Baseline, Day 30, Months 12 and 24 (sub-group of investigational sites).
8. Functional outcome: comparison of the ankle brachial index (ABI) measurement at Baseline, within 30 days after index procedure, then at Months 12 and 24.
9. Functional outcome: comparison of the Walking Impairment Questionnaire at Baseline, within 30 days after index procedure, then at Months 12 and 24.
10. Stent integrity measured as freedom from stent fracture, defined as clear interruption of a stent strut observed in a minimum of two projections, determined by core lab examination of X-rays taken with the leg in extension at 12, 24 and 36 Months.

[redacted]

4.4 Eligibility Criteria

Subjects are required to meet ALL the following criteria in order to be included in this clinical trial:

4.4.1 Inclusion Criteria

1. Subject is male or female, with age >18 and ≤85 years at date of enrollment.
2. Subject or authorized representative provides written informed consent before any study-specific investigations or procedures.
3. Subject is willing to undergo all follow-up assessments according to the specified schedule over 36 months.
4. Subject is a suitable candidate for angiography and endovascular intervention and, if required, is eligible for standard surgical repair.
5. Subject has symptomatic peripheral arterial disease (PAD) of the lower extremities requiring intervention to relieve de novo obstruction or occlusion of the native femoropopliteal artery.
6. Subject has PAD classified as Rutherford clinical category 2, 3 or 4.
7. Subject has documented PAD by either (i) a resting ankle-brachial index (ABI) of ≤0.90 (or ≤0.75 after exercise of the target limb). Resting toe brachial index (TBI) is performed only if unable to

[redacted]

reliably assess ABI. TBI must be <0.70; or (ii) Normal ABI with angiographic or ultrasound evidence of ≥60% diameter stenosis.

4.4.2 Angiographic Inclusion Criteria:

8. Subject has single or multiple stenotic or occlusive lesions within the native femoropopliteal artery ("target lesions") that can be crossed successfully with a guidewire and fully dilated. (Note: multiple target lesions must be treated as a single lesion.)
9. Single or multiple target lesions must be covered by a single stent or two overlapping stents. In the case of tandem lesions, the gap between lesions must be ≤ 3 cm.
10. Target lesion(s) eligible for treatment under the Protocol are at least 1 cm distal to the origin of the deep femoral artery and at least 3 cm above the bottom of the femur.
11. Target lesion(s) reference vessel diameter is between 4.0 mm and 6.0 mm by operator's visual estimate.
12. Single or multiple target lesions measure ≥40 mm to ≤140 mm in overall length, with ≥60% diameter stenosis by operator's visual estimate.
13. Subject has a patent popliteal artery (no stenosis ≥50%) distal to the treated segment.
14. Subject has at least one patent infrapopliteal vessel (<50% stenosis) with run-off to the ankle.

4.4.3 Exclusion Criteria:

1. Subject is unable or is unwilling to comply with the procedural requirements of the study Protocol or will have difficulty in complying with the requirements for attending follow-up visits.
2. Subject has comorbidity that in the investigator's opinion would limit life expectancy to less than 36 months.
3. Subject has iliac stent in target leg that has required re-intervention within 12 months prior to index.
4. Subject has any planned major surgical procedure (including any amputation of the target leg) within 30 days after the index procedure for this Study.
5. Subject has a target vessel that has been treated with any type of surgical or endovascular procedure prior to enrollment.
6. Subject has a target vessel that has been treated with bypass surgery.
7. Subject has PAD classified as Rutherford clinical category 0, 1, 5 or 6.
8. Subject has known or suspected active systemic infection at the time of enrollment.
9. Subject has a known coagulopathy or has bleeding diatheses, thrombocytopenia with platelet count less than 100,000/microliter or INR > 1.8.
10. Subject has a stroke diagnosis within 3 months prior to enrollment.
11. Subject has history of unstable angina or myocardial infarction within 60 days prior to enrollment.
12. Subject has a contraindication to antiplatelet, anticoagulant, or thrombolytic therapies.
13. Subject has known allergy to contrast agents or medications used to perform endovascular intervention that cannot be adequately pre-medicated.
14. Subject has known allergy to titanium, nickel or tantalum.
15. Subject has received thrombolysis within 72 hours prior to the index procedure.
16. Subject has acute or chronic renal disease (e.g., as measured by a serum creatinine of >2.5 mg/dL or >220 umol/L), or on peritoneal or hemodialysis.
17. Subject requiring coronary intervention within 7 days prior to enrollment.
18. Subject is pregnant or breast-feeding.
19. Subject is participating in another research study involving an investigational product (pharmaceutical, biologic, or medical device).
20. Subject has other medical, social or psychological problems that, in the opinion of the investigator, preclude them from receiving this treatment, and the procedures and evaluations pre- and post-treatment.

4.4.4 Angiographic Exclusion Criteria:

21. Subject has significant disease or obstruction (≥50%) of the inflow tract that has not been successfully treated at the time of the index procedure (success measured as ≤30% residual stenosis, without complication).
22. Subject has a lesion in the contralateral limb requiring intervention during index procedure or within next 30 days.
23. Subject has no patent (≥50% stenosis) outflow vessel providing run-off to the ankle.
24. There is a lack of full expansion in the predilatation balloon.
25. Target lesion(s) requires percutaneous interventional treatment, beyond standard balloon angioplasty alone, prior to placement of the study stent.
26. Evidence of aneurysm or acute thrombus in target vessel.

5.0 STUDY SCREENING AND ENROLLMENT

5.1 Subject Screening

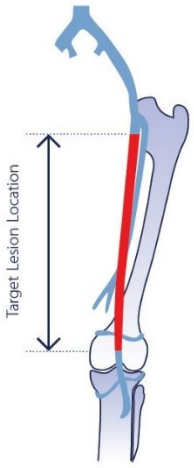

Figure 8: Location of eligible target lesions

All patients presenting to the institution with known superficial femoral and proximal popliteal artery disease requiring an interventional procedure shall be evaluated for eligibility and participation in the study. Target Lesion(s) are at least 1 cm distal to the origin of the deep femoral artery and at least 3 cm above the bottom end of the femur – see Figure 8. A member of the research team shall perform a preliminary evaluation of the potential subject's medical history and previously performed examinations to assess for initial eligibility. If the patient is willing to participate in the study, a written consent will be obtained. No study-specific requirements will be performed prior to obtaining informed consent.

5.2 Informed Consent

Written Informed Consent with the Institutional Review Board (IRB) or Ethics Committee (EC) approved consent form will be obtained for all subjects **prior** to any study-specific screening/baseline tests or procedures being performed. This does not include those procedures or tests that are obtained in the normal course of the patient's non-study related care and prior to undergoing the study procedure. The patient shall be given adequate time to read the informed consent form, have the study procedures explained, including the risks, benefits and follow-up requirements prior to signing the Informed Consent documents. All subjects providing informed consent are to receive copies of their signed informed consent documentation. The consent process may be obtained up to 14 days prior to index / treatment procedure.

5.3 Subject Enrollment

All patients requiring angioplasty due to reasons detailed in this Protocol are potential study candidates and shall be screened for eligibility. Every effort will be made to ensure eligibility prior to enrollment. According to ISO 14155:2011, enrollment in the study occurs at the time of informed consent; however, for the purposes of this study, only subjects who are consented and meet all the study inclusion criteria and none of the study exclusion criteria and are treated or treatment is attempted with the study device will be considered enrolled into the study. Therefore, the enrollment date (Day 0) will be the date of the study index procedure; the enrollment date will not be the date of informed consent for this study. Subjects who do not meet all inclusion and exclusion criteria (e.g., including: (i) operator is unable to successfully cross the target lesion with a guidewire or successfully dilate the lesion; (ii) either target reference vessel diameter or target lesion length are outside the eligible parameters; (iii) lack of patent popliteal and tibioperoneal arteries in the target limb, etc.) will be considered an angiographic screen failure and will not be followed in the study (no data will be collected on these subjects). Subjects in whom the BioMimics 3D Stent System is inserted into the vasculature and the treatment of the target lesion is attempted, but the procedure is aborted without delivery of a stent, will be followed for 30 days after the attempted index procedure. At the 30-day follow-up visit, these subjects will be assessed for safety only and the subject will be allowed to exit the study. No additional study required assessments shall be collected.

Subjects who are enrolled and treated, but who are later discovered to not meet all of the study criteria will remain in the study and complete all of the study testing and follow-up requirements. A Protocol Deviation will be completed for study subjects who are found to be ineligible after enrollment.

5.4 Subject Withdrawal

Subjects may withdraw at any time from the clinical trial without jeopardy or prejudice. If a subject prematurely terminates from the study, the reason for study termination will be recorded and the results will be tabulated by number and percent for each category. If termination is a result of an adverse event or death, an Adverse Event Form will also be completed. Subjects who withdraw consent after treatment will have their data evaluated until the time of their withdrawal.

The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, the subject completes the study, or the adverse event is otherwise explained.

All reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to loss to follow-up, withdrawal, or non-adherence with required assessments. Three attempts shall be made to contact subjects who do not return for study follow-up visits. The final attempt shall include a certified letter to the subject regarding study participation. If these subjects cannot be located, they will be considered lost to follow-up. If they are contacted but refuse to return for visits, they will be considered withdrawals. If they actively request to withdraw from the study, they will be considered withdrawals. Subjects shall be encouraged to complete a final study exit visit at the time of withdrawal to assess for safety. Data collected up to the time of loss to follow-up or withdrawal will be maintained in the study database and used for analysis purposes, as appropriate. These subjects will not be replaced.

5.5 Anticipated Total Enrollment

Two hundred eighty (280) subjects will be enrolled, anticipating 230 subjects evaluable at 12 month assessment time point. Up to 40% of total study population may be enrolled outside the United States. A minimum of 30 evaluable subjects is required in Japan for the 12 month assessment time point. No site may enroll more than 35 subjects.

6.0 STUDY PROCEDURES

6.1 Visit Schedule

Study participation will last for a total of 36 months (± 60 days). Subjects will be enrolled in the acute phase of the study. Study visits and data collection during the acute phase will be completed at index hospitalization, 30 days (± 7 days), and 12 months (365 days ± 30 days). A long-term follow-up visit will be performed at 24 months (730 days ± 60 days). A final post-market surveillance follow-up visit will be performed at 36-months (1095 days ± 60 days).

A summary schedule of the required study tests and evaluations is in Table 7.

Table 7: MIMICS-2 study schedule

Assessment	Baseline[1]	Day 0 Index Procedure (Enrollment / Treatment)	Day 30 (± 7 days)	Month 12 (365 days ± 30 days)	Month 24 (730 days ± 60 days)	Month 36 (1095 days ± 60 days)[8]
Informed Consent	X[2]					
Medical History / Physical Exam[3]	X		X	X	X	
Laboratory Assessments: Creatinine, platelets	X					
Coagulation Studies: PT/ INR[4]	X					
Urine pregnancy test if female[5]	X					
Ankle Brachial Index (ABI) [or Toe Brachial Index (TBI), if indicated]	X		X	X	X	
Rutherford Clinical Category (RCC)	X		X	X	X	
Walking Impairment Questionnaire (WIQ)[10]	X		X	X	X	
Six-Minute Walk Test (6MWT) (subgroup only)	X		X	X	X	
Index Angiogram / Stent Deployment		X				
Medications: Aspirin / Clopidogrel[6]		X	X[6]	X[6]	X[6]	X[6]
Duplex scan		X[7]		X	X	X[7]
X-rays of treatment area				X	X	X[9]
Adverse Event Assessment	X	X	X	X	X	X

[1] Standard of care evaluations may be done up to 30 days before the procedure. Protocol-specific exams that are non-standard of care cannot be obtained until after informed consent.
[2] Consent to be obtained within 14 days prior to enrollment.
[3] Medical History is required at baseline only. Refer to applicable Protocol section for physical exam requirements.
[4] PT/INR to be obtained only if subject is on chronic warfarin therapy.
[5] Negative pregnancy test within 14 days of enrollment for women of childbearing potential.
[6] Dual anti-platelet therapy is required through 30 days and then continued per physician / institutional standards of care. Aspirin therapy is to be continued indefinitely.
[7] Post-procedure duplex ultrasound will be obtained post-procedure through Day 30 (+7 days). Duplex ultrasound at 36 months only if clinical signs or symptoms are present suggestive of worsening claudication.
[8] 36-Month surveillance visit may be completed via clinic or telephone visit.
[9] The requirement for X-ray imaging may be fulfilled at a facility remote to the investigational site.
[10] WIQ may be obtained 30 days prior to index procedure through the peri-procedural period (e.g., within 24 hours of index procedure.)

6.2 Baseline

The following examinations and tests will be performed. For those study procedures that are not considered standard of care (performed only for study participation), they will be performed after the subject signs the informed consent form in order to meet **all** inclusion and **no** exclusion criteria. These examinations and tests will be used both to screen eligible subjects and provide baseline information for those subjects that meet study eligibility criteria.

All tests must be completed within the 30 days prior to undergoing the index / study procedure, except for the urine pregnancy test which must be completed within 14 days of the procedure.

- Demographic information and medical history including risk factors
- Physical examination
  - Height and weight
  - Ankle Brachial Index (ABI) or Toe Brachial Index (TBI)
  - Rutherford Clinical Category
  - Target review of symptoms, including distal pulse assessment on the target limb
- Walking Impairment Questionnaire (may be obtained 30 days prior to index procedure through the peri-procedural period, e.g., within 24 hours of index procedure)
- Six-Minute Walk Test (subgroup of US investigational sites only)
- Laboratory Assessments:
  - Platelets and creatinine
  - Coagulation profile: PT & INR if subject on chronic warfarin therapy
  - Urine pregnancy test if female of child-bearing age (within **14** days of procedure)

6.3 Medications

Table 8 provides a summary of the Study required medications, dosage and timing:

Table 8: Summary of Protocol-required medications for MIMICS-2 Study

Medication	Peri-Procedure (± 24 hours of Index Procedure)	Intra-Procedure	Post-Procedure
Aspirin	Minimum loading dose of 75 mg required, if not on chronic aspirin therapy	N/A	A minimum of 75 mg per day indefinitely
Clopidogrel (or similar antiplatelet agent)	Minimum loading dose of 300 mg required, if not on chronic clopidogrel therapy	N/A	Clopidogrel 75 mg per day for a minimum of 30 days (or per prescribing dose if other similar antiplatelet agent)
Heparin / Bivalirudin	N/A	Maintain anticoagulation per hospital / institution standard of care	N/A

6.4 Index Procedure

At the index procedure, a radiopaque ruler is to be placed directly on the subject's leg under the sterile drapes. The end of the ruler is placed at the tibial tubercle. The ruler will serve as a location marker for the target lesion(s) being treated at both the index procedure and as a reference point for follow-up examinations, including follow-up duplex evaluations. All other measurements are referenced back to this angiographic measurement.

Angiography for final anatomic eligibility will be obtained at time of index procedure prior to opening the stent package and inserting into the vasculature. The baseline index procedure angiogram is to be performed as per guidelines established by the core lab.

Reminder: Subjects that do not meet the angiographic eligibility criteria will be documented as an angiographic screen failure and will not be considered enrolled into the study; no data collection will be obtained on these subjects. Only subjects that meet eligibility criteria will be enrolled into the study and will undergo stent placement. All consented, screen failed, and enrolled and treated subjects will be recorded on the Screening & Enrollment Log.

6.4.1 Pretreatment of Lesion / Vessel

The Target Lesion must be successfully crossed and fully pre-dilated with standard percutaneous transluminal balloon angioplasty. This Protocol does not allow for direct stenting. In general, a gentle pre-dilatation with a fully-expanded balloon catheter that is the same size as the reference vessel diameter (RVD) (i.e., 1:1 balloon to artery ratio) is required. Pre-treatment therapies other than PTA (such as, but not limited to, drug-eluting balloon therapy, directional atherectomy, excimer laser, rotational atherectomy, etc.) are not permitted in this trial.

6.4.2 Implant Procedure

Refer to the Instructions for Use (IFU) for a description of the implant procedure. Additional data captured during the procedure include, but may not be limited to:

- Baseline angiographic criteria assessment, i.e., inflow disease, outflow disease, patent tibial, etc.
- Location of stent placement using angiographic radiopaque ruler during index procedure
- Assessment of post-stent implantation lumen patency via angiogram at the conclusion of the index procedure (percent angiographic stenosis and angiographic patency of ≤50% stenosis at target site)
- Evaluation of total procedure time
- Determination of blood loss and replacement
- Identification of technical difficulties
- Adverse event observation, evaluation, and treatment
- At the conclusion of the index procedure, an angiographic cine showing the stent with reproducible landmarks for follow-up evaluation and assessment. In addition, a final distal run-off cine to the ankle shall be performed (per Angiographic Core Lab Protocol) to assess for procedural- and/or device-related complications.

6.4.3 Stenting

The stenting procedure should be performed according to the Instructions for Use. Lesion length per inclusion criteria is between 40 mm and 140 mm. This can be a single lesion or multiple tandem lesions; however, the total lesion length may not exceed 140mm. No more than two (2) study stents may be used to treat the lesion(s) as stated in the inclusion and exclusion criteria. If the total lesion length is less than or equal to 140 mm, then a single primary study stent should be used (maximum stent length is 150 mm).

6.4.4 Additional Stenting / Bailout Procedures

If the first BioMimics 3D stent does not cover the entire lesion and an additional stent is needed (e.g., due to lesion length, geographic miss, inaccurate visual assessment of lesion length), a second BioMimics 3D stent of appropriate size and length must be used to cover the lesion. No other investigational or commercially available stents may be used. Overlapping of stents should be limited to no greater than 10 mm.

If a study subject experiences a major edge dissection or an occlusive complication manifested as decreased target vessel flow or ischemic changes which do not respond to repeat balloon inflations, intra-arterial vasodilators (nitroglycerin, verapamil) or fibrinolytic agents, the investigator shall

perform a prolonged balloon inflation of at least 3 minutes. If the additional prolonged balloon inflation is not successful in treating the complication and an additional stent is warranted (bail-out stent), a BioMimics 3D stent of appropriate size and length should be used. No other investigational or commercially available stents may be used. Overlapping of stents should be limited to no greater than 10mm.

6.4.5 Post-Treatment of Lesion / Vessel

The target lesion must be post-dilated with standard percutaneous transluminal balloon angioplasty. In general, a post-dilatation ratio of 1:1 between the balloon and the reference vessel diameter is required. Caution should be employed to ensure post-dilatation is accomplished within the stented region to minimize tissue injury outside of the stent margins.

6.5 Day 30 Follow-Up

The following evaluations will be scheduled for **Day 30** (± 7 days) post procedure:

- Physical examination
  - Rutherford Clinical Category
  - ABI or TBI
  - Target review of symptoms, including distal pulse assessment on the target limb
- Walking Impairment Questionnaire
- Six-Minute Walk Test (subgroup of US investigational sites only)
- Duplex ultrasound (may be performed anytime following the index procedure through the Day 30 visit)
- Adverse event assessment

6.6 Month 12 Follow-Up

The following evaluations will be scheduled for **Month 12** (365 days ± 30 days) post procedure:

- Physical examination
  - Rutherford Clinical Category
  - ABI or TBI
  - Target review of symptoms, including distal pulse assessment on the target limb
- Walking Impairment Questionnaire
- Six-Minute Walk Test (subgroup of investigational sites only)
- Duplex ultrasound
- X-rays of the target limb in extension (those US sub-study sites participating in the Exploratory Outcome study into swirling flow will also conduct bent-knee X-ray imaging)
- Adverse event assessment

6.7 Month 24 Follow-Up (Long-Term Follow-Up Phase of the Study)

The following evaluations will be scheduled for **Month 24** (730 days ± 60 days) post procedure:

- Physical examination
  - Rutherford Clinical Category
  - ABI or TBI
  - Target review of symptoms, including distal pulse assessment on the target limb
- Walking Impairment Questionnaire
- Six-Minute Walk Test (subgroup of investigational sites only)
- Duplex ultrasound
- X-rays of the target limb in extension
- Adverse event assessment

6.8 Month 36 Follow-up (Post-Market Surveillance Phase of the Study)

This visit may be conducted as a telephone or clinic visit as long as the subject is able to obtain the final follow-up X-rays per the study requirements. The final X-ray imaging may be fulfilled at a facility remote to the investigational site as long as the study and core lab instructions and requirements are followed. The following evaluations will be scheduled for **Month 36** (1095 days ± 60 days) post procedure:

- X-rays of the target limb in extension
- Duplex ultrasound (required only if clinical signs or symptoms are present suggestive of worsening claudication)
- Adverse event assessment

7.0 ADVERSE EVENTS

All adverse events will be recorded and documented throughout the 12-month visit. Following the 12-month visit, only major adverse events (MAE), serious adverse events (SAE), revascularizations in target leg, and unanticipated adverse device effects (UADE) will be recorded and documented through the 36-month follow-up visit.

The Investigator at each participating center is ultimately responsible for reporting adverse events to the Sponsor. The adverse event electronic case report form (eCRF) provides a venue for the Investigator to record any adverse event data. The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, the subject completes the study, or the adverse event is otherwise explained.

The Sponsor shall review all adverse events for their relationship to the study device(s) and/or procedures and comparative anticipated safety event rates. The Sponsor will conduct evaluations of any unanticipated device-related event per standard operating procedures.

7.1 Adverse Event

For the purposes of this study, an adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, whether or not related to the investigational device or procedure. In addition, the definition of AE applies to any event with an onset during enrollment / index procedure or to any underlying diseases, present at baseline, that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. This definition includes events occurring during the follow-up period.

All reported AEs through 12 months must be recorded in the electronic database. Following the 12 month visit, only SAEs, MAEs, revascularizations in target leg, and UADEs will be recorded in the electronic database. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE, the study device and the study procedure.

The following definitions for rating severity of adverse events will be used:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.

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.

Adverse Device Effect (ADE) / Device-Related Adverse Event: an adverse device effect (or device-related adverse event) is defined as any untoward adverse effect when, in the judgment of the Investigator, the clinical event has a reasonable time sequence associated with use of the investigational device and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the device directly caused or contributed to the adverse event.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from user error or from intentional misuse of the investigational medical device.

Major Adverse Vascular Event (MAVE): a major adverse vascular event is an adverse event that could possibly be procedure- or device-related. MAVE is defined as the following:

- Abrupt occlusion
- Access site complication requiring surgery or transfusion
- Arterial perforation or rupture
- Dissection (Grade C or greater) in target vessel requiring intervention
- Embolization, distal
- Limb ischemia
- Necrosis, target limb
- Pseudoaneurysm, access site
- Pseudoaneurysm, target limb
- Restenosis, target lesion
- Restenosis, target vessel
- Thrombosis

Procedure-Related Adverse Event*:* an adverse event is considered to be procedure-related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the assigned study procedure and is not specific to the investigational device (i.e., BioMimics 3D Stent System) used. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

Concomitant Medication-Related Adverse Event: an adverse event is considered to be concomitant medication-related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with concomitant medications used in conjunction with the investigational device and is not otherwise specific to the investigational device (e.g., bleeding associated with anticoagulation medication).

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the subject's pre-existing condition and is not specific to the investigational device or procedure. Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device-related or procedure-related.

Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Veryan or its designee, in cooperation with the Investigator, will assess all adverse events considered to be device-related for potential reportability to the FDA and other regulatory authorities (as applicable) as an UADE.

Events Not Considered Adverse Events

For purposes of this study, the following events are not considered adverse events, because they are normally expected to occur in conjunction with endovascular procedures / post-procedure, or are associated with customary, standard care of subjects undergoing these procedures:

- Early post-operative pain (within 24 hours post-index procedure) at the access site and/or related to position on procedure table
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 hours post-index procedure)
- Chest pain without associated ECG changes

- Hematocrit decrease from baseline not associated with hemodynamic changes, remaining above 26% and not requiring transfusion
- Electrolyte imbalance without clinical sequelae following endovascular procedure, even if requiring correction
- Low grade temperature increase (≤38.3 °C/≤101 °F)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Any pre-planned surgical procedures

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences, and may decide that the above events should be reported as adverse events.

7.2 Serious Adverse Event (SAE)

A serious adverse event is defined as an adverse event that:

- Led to death,
- Led to a serious deterioration in the health of the subject, that either resulted in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient hospitalization or prolongation of existing hospitalization
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

All Serious Adverse Events will be reported throughout the study.

NOTE: Planned hospitalization for a pre-existing condition or elective cosmetic procedures, or a procedure required by the investigational plan without serious deterioration in health, is not considered a serious adverse event.

All SAEs must be reported to the IRB / EC in accordance with IRB / EC reporting requirements and institutional policies. The Investigator will note whether the adverse event was device-related or procedure-related and the severity of the event. All SAEs must be reported by the Investigator (or designee) to the Sponsor within 24 hours of knowledge of the event, or by the end of the next working day.

7.3 Major Adverse Event (MAE)

For the purposes of this study, the definition of a major adverse event includes:

- Death
- Any major amputation performed on the target limb
- Clinically-driven target lesion revascularization

All MAEs and suspected MAEs must be reported by the Investigator (or designee) to the Sponsor within 24 hours of knowledge of the event, or by the end of the next working day, and will be reviewed by the Clinical Events Committee. Those events confirmed by adjudication as MAEs will comprise the composite safety endpoint for major device-related adverse events.

7.4 Adverse Event Reporting Requirements

7.4.1 General Reporting Requirements

All serious and potentially device- and/or procedure-related adverse events must be recorded on the Adverse Event electronic CRF by the Investigator (or designee). The report should include: severity,

duration, action taken, treatment outcome and relationship of the adverse experience to the study device, procedure, concomitant medications, pre-existing condition, (i.e., unrelated, related or relationship unknown).

In the case of serious adverse events, procedure- and /or device-related adverse events, and device malfunctions and failures, medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging, or lab studies) must be provided to the Sponsor or its designee.

7.4.2 Reporting Requirements for Serious and Major Adverse Events

All serious *and* major adverse events must be reported by the Investigator (or designee) to the Sponsor within 24 hours of knowledge of the event or by the end of the next working day. This may be done via phone, fax, email or electronic data capture for the clinical database.

The Investigator (or designee) shall send a written report including a narrative description of the serious *or* major adverse event to the Sponsor or their designee within five (5) working days of the initial report. This can also be in the form of the AE eCRF.

Any serious or major adverse events and all deaths regardless of cause must also be reported to the IRB / EC per local IRB / EC requirements. It is the responsibility of the Investigator to inform their IRB / EC of these serious adverse events as required by their IRB / EC procedures and in conformance with FDA and local regulatory requirements. In addition, the investigator shall provide documentation of the IRB / EC report to Veryan or its designee.

All adverse events (AE) will be monitored from the time of enrollment through the 12-month assessment. SAEs, MAEs, revascularizations in target leg, and UADEs will be monitored from the time of enrollment through the follow-up period for this trial. A description of the event, including the start date, resolution (or date of final outcome assessment) date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE, SAE or MAE and the study treatment. Pain, neurological status and functional impairment should be considered AEs when a subject's complaint for any of these symptoms is outside the normal pattern for the illness treated.

All AEs should be followed until the event is resolved or judged to be chronically stable. The clinical site should plan to provide relevant AE follow-up information to the Sponsor upon request.

The Sponsor or its designee will report all applicable serious adverse events as vigilance reports per MEDDEV 2.12.1, Rev 8 (2013) "Guidelines on a Medical Devices Vigilance System" and as clinical study reportable events per MEDDEV 2.7/3 "Clinical Investigations: Serious Adverse Event Reporting". The Sponsor will determine whether all of the local Investigators need to be informed immediately of an SAE or UADE, or whether this can be postponed until the next regularly scheduled study update.

7.4.3 Device Failures and Malfunctions

All reported device observations / performance issues, malfunctions or failures of the Veryan BioMimics 3D stent are required to be documented in the eCRF. In the event of a suspected observation or device problem, the investigational device shall be returned to the Sponsor for analysis. Device failures and malfunctions should also be documented in the subject's medical record. Instructions for returning the investigational device are included in the Manual of Operations Binder.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual manner on the AE eCRF.

8.0 RISK/BENEFIT ASSESSMENT

8.1 Risks to the Subject

8.1.1 Risk Analysis

The BioMimics 3D Stent System or the MIMICS-2 Study treatment procedure may result in failures or complications similar to other peripheral stents with similar indications for use. Prior human use and preclinical studies of the BioMimics 3D Stent System have not shown any additional risks. Documented risks of peripheral stents and/or the treatment procedure include, but are not limited to (potential risks are listed in alphabetical order and not per risk level):

- Access-site complications
- Allergic reaction to contrast media / medications
- Aneurysm
- Arterial dissection
- Arterial perforation
- Arterial rupture
- Arterial spasm
- Arteriovenous fistula
- Bleeding complications
- Cardiac arrest
- Cardiac arrhythmia
- Death
- Device embolization
- Device malfunction
- Embolism and/or arterial thrombosis
- Emergency or non-emergency arterial bypass surgery
- Extravasation of contrast media
- Fracture of the guide wire or any component of the device that may or may not lead to device embolism, serious injury or surgical intervention
- Gastrointestinal bleed
- Hematoma
- Hypotension
- Infection or fever
- Ischemia
- Myocardial infarction or coronary ischemia
- Neurological deficit
- Placement of a bailout stent
- Pseudoaneurysm
- Radiation exposure
- Reaction to contrast media / medication
- Renal insufficiency or failure
- Respiratory distress or failure
- Restenosis of the treated segment
- Serious injury requiring surgical intervention
- Stent strut fracture(s)
- Stroke or TIA
- Thrombosis
- Transfusion
- Total occlusion of the peripheral artery

- Vascular complications which may require surgical repair (conversion to open surgery)
- Worsening of peripheral arterial disease

These risks are present in any endovascular treatment procedure for which the study subjects would be indicated because of their disease, and the subject's physician will review these risks with the subject. Standard of care practice should be followed for preparing a subject for endovascular intervention, including medication and vascular access.

8.1.2 Risk Minimization

As with any endovascular procedure, appropriate safety precautions will be followed. In addition, this Protocol provides additional steps to minimize risk to study subjects. These include the following:

- **Investigator Selection**: The Investigators in this study are selected based on their experience in treating subjects with peripheral arterial disease (PAD) and performing peripheral endovascular treatment procedures, including stent placement and peripheral balloon angioplasty.
- **Investigator Training**: Investigators will be trained in proper device operation prior to study start. Training will include didactic and hands-on training with the Veryan BioMimics 3D Stent System (e.g., bench-top model).
- **Subject Screening**: This Protocol includes appropriate precautions in subject selection. For example, subjects with known sensitivity to contrast or other agents used in the study with significant co-morbidities or uncontrolled cardiovascular or other disease will be excluded.

Subjects with excessive tortuous vascular anatomy, known allergy to nickel, and/or unable to take standard medications used for interventional procedures (e.g., anticoagulants, contrast agents, and antiplatelet therapy) will be excluded from this Protocol per IFU Contraindications for Use.

8.2 Potential Benefits

Prior human clinical experience in a population of 60 subjects has validated that the Veryan device can be used to safely and effectively stent the femoropopliteal arteries, resulting in acute and long term luminal patency. The MIMICS-2 trial is intended to evaluate the safety and effectiveness of the BioMimics 3D Stent System in a larger clinical population.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Analysis Populations

- *Intention-to-Treat (ITT) Analysis Set*: includes all enrolled subjects.
- *Modified Intention-to-Treat (mITT) Analysis Set*: includes all enrolled subjects in whom the BioMimics 3D Stent is implanted. Those subjects in whom the procedure is aborted without deployment (implantation) of a stent are excluded in this analysis set. This is the primary analysis set for the primary safety and effectiveness endpoints, as well as secondary and exploratory endpoints.
    - While mITT is intended as the primary analysis set for all safety and effectiveness endpoints, the primary safety and effectiveness endpoints will additionally be evaluated in the ITT analysis set as supportive information. All subjects excluded from mITT analysis set will be described in the final study report and the reasons for aborted procedures, if any, detailed.

9.2 Population Demographics

The demographics and medical history will be presented in tabular form for all subjects enrolled in this study (ITT analysis set). Means, standard deviations, and sample size will be used to summarize continuous characteristics such as age. Percentages, raw number of subjects exhibiting a characteristic, and sample size will be used to summarize categorical characteristics such as gender. Demographic and medical history data will be additionally tabulated for the mITT analysis set.

9.3 Primary Endpoint Analysis

Endpoints will be analyzed using the modified intention-to-treat analysis set as described below. The study will be considered successful if both primary safety and efficacy endpoints have been met. An additional supportive analysis will be conducted in the ITT analysis set for the primary safety and effectiveness endpoints.

9.3.1 Primary safety endpoint:

The primary outcome measure for safety is the composite of MAE as adjudicated by the CEC including death, any major amputation performed on the target limb or CDTLR through 30 days. The one-sided lower 97.5% Agresti-Coull confidence bound will be computed for the composite and compared to the safety performance goal of 88% for bare Nitinol stenting as defined by the VIVA Physicians Inc. [38]. The performance goal will have been met if the lower bound is greater than 88%. This analysis will be conducted in the mITT analysis population. Only subjects with sufficient follow-up data will be included. That is, only subjects with ascertainment of status past the lower window for the 30-day visit (with any ascertainment of status post 23 days on study) and/or subjects who experienced an MAE at any time prior to and including 30 days will be considered eligible for this analysis. Any ascertainment of status post 23 days includes subjects who may have had missing safety status at 30 days, but are found to be free of MAE at a later out-of-window date. This subject will be considered MAE-free at 30 days. It is not expected that there will be notable loss to follow-up at this time point, however, if any loss to follow-up is present, sensitivity analyses for excluding these data will be conducted as described in Section 9.9 below.

9.3.2 Primary effectiveness endpoint:

The primary outcome measure for effectiveness is primary stent patency rate at 12 months as defined in 4.1.2. The one-sided lower 97.5% Agresti-Coull confidence bound will be computed for patency and this lower bound will be compared to the effectiveness performance goal of 66% for bare Nitinol stenting as defined by the VIVA Physicians, Inc.[38]. The performance goal will be met if the lower

bound is greater than 66%. The mITT analysis population will be used for this endpoint; however, only subjects with valid endpoint data without imputation will be included. This includes all subjects with imaging data at 12 months and/or subjects without imaging data who experienced a CDTLR. Additionally, if a subject is missing stent patency status at the 12 month visit but is found to be patent at a later out-of-window date, the subject will be considered patent at 12 months. Sensitivity analyses for excluding missing data will be conducted as described in Section 9.9 below.

9.4 Secondary Endpoint Analysis

All secondary endpoints as described in Section 4.2 will be tabulated. Means, standard deviations and sample size will be used to summarize continuous characteristics. Distributions of continuous data will be examined and if non-normality is exhibited, medians and interquartile ranges will be presented. Percentages, raw number of subjects exhibiting a characteristic, and sample size will be used to summarize categorical characteristics. Measures collected serially over time (for example, ABI) will be presented at each time point, and the measure at each time point will be compared to the baseline measure as well as tested for trends. All available data will be used for each endpoint and no imputations will be done. The mITT analysis set will be used for these analyses.

[redacted]

9.6 Other Safety Data

All adverse events, serious adverse events, major adverse events, and UADEs will be tabulated for the ITT analysis set and provided in listings. Device failures and malfunctions will be provided in a separate listing. Relevant concomitant medications will be tabulated at each study time point and all collected medications will be provided in listings.

9.7 Site Poolability and Subgroup Analyses

Poolability of study subjects across investigational sites will be explored by comparing the primary outcome measure across site. Initially, testing of the primary outcomes will be conducted across site at a two-sided alpha=0.15 level using a chi-square test, unadjusted for covariates. If differences between sites exist at the alpha=0.15 level, further analysis will compare prognostic factors, protocol violations and study outcomes across sites using a chi-square test for categorical data and t-test for continuous data. For these analyses, any sites with fewer than 10 subjects will be pooled by country. Within the US, sites will be pooled by region (Northeast, Southeast, Midwest and West). If a country/region has fewer than 10 subjects, that country/region will be pooled with its nearest neighboring country/region. Regardless of these findings, if differences between sites exist at the alpha=0.15 level, summary statistics will be presented for each site. Any differences by study site will be discussed in the study report. If substantial differences emerge, a sensitivity analysis of the primary outcomes may be performed by excluding outlying sites from the analysis.

Additionally, an analysis by region (US vs. OUS) will be conducted for the primary endpoints. Heterogeneity of region will be tested via a chi-square test. If no statistically significant difference exists for the primary endpoints at alpha=0.15, the data will be considered poolable by region. If a statistically significant difference exists for the primary endpoints at alpha=0.15, the primary endpoints will be presented by region along with 95% confidence intervals. If difference between region exist but can be explained by baseline covariates, then the data will be considered poolable by

region, however, descriptive statistics will be presented by region as noted above and discussed in the study report.

Heterogeneity of the primary endpoints will also be explored for the subgroup sex (Male vs. Female). Outcomes will be reported separately for each group along with 95% confidence intervals. A chi-square test will be conducted to determine if a statistically significant difference (at alpha=0.15) exists between the groups. If no statistically significant difference exists, then the results will be considered poolable by sex. If difference between sexes exist but can be explained by baseline covariates, then the data will be considered poolable by sex, however, descriptive statistics will be presented by sex as noted above and discussed in the study report.

The results of the subgroup analyses for region (US vs. OUS) and sex will be presented in the final study report regardless of the findings above. Descriptive statistics will be presented by subgroup including frequency and percent. The study is not powered for these subgroups, however, so these analyses are considered exploratory. While it is expected that some differences between these groups will exist, any statistically significant (at alpha=0.15) and/or clinically meaningful (or clinically unexpected) differences between subgroups will be reported along with the primary results. No formal statistical inference will be made within subgroups with respect to the performance goal for labeling purposes, only descriptive statistics will be presented. As no formal inference regarding subgroups will be made, no adjustment for multiplicity is indicated.

Primary endpoints will be reported separately for the following subgroups:

- subjects who are taking cilostazol (vs. not taking cilostazol),
- Japan versus rest of world (ROW) and versus the overall study cohort,
- Japan versus US versus Germany,
- subjects implanted with a 5 mm stent diameter versus > 5 mm stent diameter.

In addition, the effect of overlapping stents will be explored by looking at patients with single versus multiple stents.

While these subgroups are not powered statistically to detect meaningful differences, the data will be presented and any perceived differences will be described in the final study report.

9.8 Sample Size

Using Percutaneous Transluminal Angioplasty (PTA) data from a series of clinical studies, VIVA Physicians Inc., developed performance goals that may be used as standards of comparison for safety and effectiveness in the treatment of claudication associated with femoropopliteal disease. The safety and effectiveness of the BioMimics 3D stent will be compared to the VIVA Physicians' defined objective performance goals (OPGs).[38]

- VIVA Physicians' primary safety endpoint is freedom from major adverse events (MAE), defined as all-cause death, index limb amputation and target lesion revascularization (TLR), through 30 days. The lower limit of the one-sided 95% confidence interval of the true femoropopliteal PTA rate for freedom from MAE was 88%, which was established as the primary safety OPG.
- The VIVA Physicians Inc. primary effectiveness endpoint is the primary stent patency rate at 12 months, where patency is defined as freedom from more than 50% restenosis based on DUS peak systolic velocity ratio (PSVR) comparing data within the treated segment to the proximal normal arterial segment. A PSVR > 2.0 is indicative of the loss of patency. The primary effectiveness OPG of 66% was established as two times the observed PTA freedom from loss of patency rate of 33%.

Sample size estimation for the MIMICS-2 Study was performed using VIVA OPGs and outcomes from the Mimics Study, a first-in-man study of the safety and effectiveness of the BioMimics 3D Stent System conducted at eight investigational sites in Germany in which patients were followed for 24 months after the index procedure.

There are two primary endpoints in the MIMICS-2 Study, one safety and one effectiveness. In order for the trial to be considered successful, both primary endpoint hypotheses must be satisfied, thus no adjustment for alpha is necessary. The size of the study will be driven by the primary effectiveness endpoint as detailed below. Initially, powers of 95% and 85% are considered for primary safety and effectiveness, respectively, in order to preserve an overall power greater than 80%.

Primary Safety Endpoint and Hypothesis Test

The primary safety endpoint in the MIMICS-2 Study is a composite of Major Adverse Events (MAE) including all-cause death, any major amputation performed on the target limb, or CDTLR through 30 days.

The primary safety objective is to demonstrate that the freedom from MAE rate for treatment with the BioMimics 3D Stent System meets the VIVA OPG of 88%. The null and alternative hypotheses are as follows:

$$H0: \pi \leq 88\%$$

$$HA: \pi > 88\%$$

where π is the population proportion of subjects treated with BioMimics 3D who are free from MAE through 30 days. Hypothesis testing will be conducted using the confidence interval approach. Success on the primary safety objective will be established if the one-sided lower 97.5% Agresti-Coull confidence limit [40] for the proportion of subjects treated with BioMimics 3D who are free from an MAE through 30 days is greater than 88%.

Sample size implications for Primary Safety Objective

The sample size for the primary safety objective was determined using the method presented in Agresti-Coull [40]. The freedom from MAE rate in the Mimics Study was 100% at 30 days, so a conservative estimate of 98% freedom from MAE in the MIMICS-2 Study was used for sample size calculations.

The following assumptions were used for sample size:

- 95% statistical power.
- Confidence interval approach to hypothesis testing with one-sided 97.5% lower Agresti-Coull confidence limit (one-sided type-I error rate of 2.5%).
- VIVA freedom from MAE OPG of 88%.
- Estimated 98% freedom from MAE in MIMICS-2.

The conclusion was that 83 evaluable subjects would be required to statistically power the primary safety endpoint at the 95% level.

Primary Efficacy Endpoint and Hypothesis Test

The primary effectiveness endpoint in the MIMICS-2 Study is primary stent patency rate at 12 months. Patency is defined as no significant reduction in luminal diameter (i.e. < 50% diameter stenosis) since the index procedure. Luminal diameter is assessed by core lab using angiography or duplex ultrasound imaging. Loss of primary stent patency is deemed when peak systolic velocity ratio (PSVR) is >2.0[redacted], or where angiography reveals >50% diameter stenosis, or where the subject undergoes clinically-driven TLR. When both imaging modalities are available, angiography takes precedence.

[redacted]

The primary effectiveness objective is to demonstrate that the 12-month primary stent patency rate after use of the BioMimics 3D Stent System is statistically superior to the VIVA OPG of 66%. The null and alternative hypotheses are as follows:

$$H0: \pi \leq 66\%$$

$$HA: \pi > 66\%$$

where π is the population BioMimics 3D patency at 12 months. Hypothesis testing will be conducted using the confidence interval approach. Success in the primary effectiveness objective will be established if the one-sided lower 97.5% Agresti-Coull confidence limit for the proportion of subjects treated with BioMimics 3D that continue to have treated segment patency through 12 months is greater than 66%.

Sample size implications for Primary Efficacy Objective

The sample size for the primary effectiveness objective was determined using the method presented in Agresti-Coull. The 12-month patency rate for those subjects who received BioMimics 3D stents in the randomized portion of the MIMICS Study was 75% (PSVR ≤ 2.0) with no CDTLR in the interim, and this value was used as the estimate of BioMimics 3D performance in the MIMICS-2 Study.

The following assumptions were used for the primary effectiveness objective sample size calculation:

- 85% statistical power.
- Confidence interval approach to hypothesis testing with one-sided 97.5% lower Agresti-Coull confidence limit (one-sided type-I error rate of 2.5%).
- VIVA 12-month patency OPG of 66%.
- Estimated 12-month primary stent patency rate in the MIMICS-2 Study of 75%.

The conclusion was that 230 evaluable subjects would be required to statistically power the primary effectiveness endpoint at the 85% level.

Final sample size determination

In order to statistically power both of the primary endpoints simultaneously, 230 evaluable subjects at 12 months are required. In order to allow for attrition, a sample size of 280 subjects should be enrolled in the MIMICS-2 Study. Thus the power for the primary safety endpoint is actually >99%, keeping the overall study power at approximately 85%.

9.9 Handling of Missing Data

For all primary, secondary and exploratory analyses, no imputation of missing data is planned. Subjects who have ascertainment of status at a later out-of-window date (for example, subjects who are known to be free of MAE past 30 days but missed the 30 day visit) are not considered missing as their status is known and their data will be used as noted previously. A sensitivity analysis, specifically a tipping

[redacted]

point analysis, will be used to assess the impact of missing data on the study conclusions for the primary endpoints. This sensitivity analysis will be performed on the ITT analysis set.

9.10 Interim Analysis

There is no interim analysis planned with the purpose of altering the Protocol or planned statistical analyses. When all data have been collected and imaging completed for the co-primary endpoints (through 12 months), the database will be cleaned and the primary study analysis conducted. All data available at that time will be summarized for reporting and regulatory filing purposes (PMA submission on primary data set).

10.0 INVESTIGATOR RESPONSIBILITIES, RECORDS & REPORTS

The Investigators are responsible for signing the Investigator Agreement prior to the commencement of the study and for ensuring that this trial is conducted according to this study Protocol, GCPs, Declaration of Helsinki, 21 CFR Parts 50, 54, 56 and 812, ISO 14155:2011 (Section 9) and any other local, national or IRB / EC requirements that apply to Clinical Investigations at their center.

It is also the Investigator's responsibility to ensure that all sub-investigators and staff assisting with this study have the appropriate qualifications and that they complete training on the Protocol, investigational devices and study procedures, and that subject confidentiality is respected.

10.1 Informed Consent & Institutional Review Board / Ethics Committee

(21 CFR Parts 50 & 56; ISO 14155: 2011 Section 4)

Because this study is collecting medical data from subjects providing written informed consent, the Investigator at each site is responsible for securing IRB / EC approval for this study Protocol and the Informed Consent documents. The local IRB / EC for each specific institution must review and approve this study Protocol and the specific Informed Consent form to be used at that site **prior** to enrollment of the first subject. The Sponsor **must** also review and approve the final Informed Consent documents prior to their use. The Sponsor must receive a copy of any IRB / EC correspondence as well as the final approval letter and the final approved Informed Consent from each IRB / EC.

The Investigator is responsible for ensuring that all applicable local and national (21 CFR Part 50, ISO 14155:2011) requirements, and Declaration of Helsinki are met when completing the informed consent process. Written, informed consent is to be obtained for all subjects **prior** to enrollment.

The Investigator or clinical site staff will not make amendments to this Protocol or the Informed Consent form without **PRIOR** written approval from the Sponsor. All approved amendments must then be submitted to the local IRB / EC and national authorities, as appropriate for approval.

10.2 Withdrawal of Approval

If the Investigator's IRB or EC withdraws their approval to conduct this study for any reason, the Investigator **must** notify the Sponsor as soon as possible, but in no event later than **five working days** after the withdrawal of the approval.

10.3 Clinical Data Collection

Standardized electronic case report forms (eCRF) will be used to collect complete and accurate records of the clinical data from the MIMICS-2 trial according to the GCPs requirements. The Investigator and/or study staff under his/her direction is responsible for accurately recording the clinical data for this study and submitting it to the Sponsor in a timely manner.

10.4 Device Accountability

The Sponsor will ship investigational devices to the designated Investigators participating in this study following IRB / EC approval. All Investigators will be responsible for providing a secure storage location for the devices, supervising device use, and the disposal and/or return of the devices as instructed by the Sponsor. In addition, all Investigators will maintain records to document the receipt, use and disposition of all devices received by their site intended for this study. The Sponsor and/or designee will also maintain records of all shipments and disposition of the investigational devices. The Sponsor and/or their authorized Contract Research Organization (CRO) will routinely inspect the clinical site inventory records for device accountability at the clinical sites participating in this study.

10.5 Investigator Reports

10.5.1 Serious Adverse Events & Major Adverse Events

The Investigator will report to the Sponsor by telephone, email, fax, or electronic CRF submission any SAE or MAE as soon as possible (within 24 hours of the Investigator becoming aware of the event or by the end of the next working day). Additionally, SAEs and MAEs should be reported to the IRB / EC, if required per the clinical site guidelines or as directed by the Sponsor. The Adverse Event eCRF is to be completed and submitted to the Sponsor within five (5) working days of the event. The contact information for reporting SAEs and MAEs is provided in the study contact section of this Protocol.

10.5.2 Device Malfunctions or Failures

The Investigators will report any Device Malfunctions or Failures that occur, to the Sponsor within 24 hours of the Investigator becoming aware of the device malfunction or failure or by the end of the next working day. The report may be made by or within 24 hours via telephone, email or fax. The Investigator or study staff are to return the devices per the Instructions for Use for investigation. The Device Performance eCRF is to be completed and submitted to the Sponsor within five (5) working days of the event. The contact information for reporting Device Performance issues is provided in the study contact section of this Protocol.

10.5.3 Deviations from the Investigational Plan

The Investigator must notify the Sponsor of any deviation from the Investigational Plan. The Investigator should also notify the IRB / EC as required per their local requirements or as directed by the Sponsor. This notice must occur as soon as possible, but in no case longer than five (5) working days after the Investigator becomes aware of a major deviation. Major deviations include, but is not limited to, those that involve the informed consent process, the inclusion/exclusion criteria of the study, SAE/MAE reporting, device misuse or device accountability discrepancies, or any deviation that involves or leads to a serious adverse event in a study participant.

10.5.4 Investigator Final Report

The Investigator will report information and events according to the timelines in Table 9. Within three (3) months of Study completion, the Investigator will provide a final study report that summarizes their enrollment and study participation. This report should include a summary of enrollment, AEs, MAEs, SAEs, UADEs and Device Malfunctions and Failures. This report will be forwarded to the IRB / EC and the Sponsor after all of the enrolled subjects have completed their final follow-up visit or have exited the study and the study close-out visit has been completed, but no later than three (3) months following completion of the last follow-up visit.

Table 9: MIMICS-2 investigator reporting timelines

Form/Report	Submission Timeframe
Enrollment notification	Completion of Enrollment eCRF within 24 hours of enrollment, or by the end of the next working day.
Electronic CRFs	Completion within 3 working days of study visit.
Angiographic, X-Ray and Duplex Ultrasound Images	Submit to Core Lab within 3 working days of completion.
Adverse Events (non-serious)	Complete eCRF within 14 days of the Investigator becoming aware of the event.
SAEs & MAEs	Submit notification to Sponsor within 24 hours of the site becoming aware of the event, or by the end of the next working day; submit to the local IRB / EC as required or as directed by the Sponsor.
Study Progress Reports	As required by the local IRB / EC (minimum annually).
Final Report to the IRB / EC	Within 3 months of Study completion.

10.6 Publication Policies

At the conclusion of the MIMICS-2 Study, a multi-center manuscript will be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require the prior approval of Veryan. The analysis of other pre-specified and non-pre-specified endpoints will be performed by Veryan and will require pre-approval by Veryan. For the purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data and/or single-center experience reports will require approval from Veryan.

This study will be registered with www.clinicaltrials.gov.

11.0 SPONSOR RESPONSIBILITIES

As the Sponsor of this clinical study, Veryan has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration (FDA) and ISO 14155:2011 (Section 8). In this study, Veryan will have certain direct responsibilities and will delegate other responsibilities to Independent Contractors. Together, both Veryan and its Independent Contractors will ensure adherence to the sponsor's general duties (21 CFR 812.40; ISO 14155:2011 Section 8), selection of Investigators (21 CFR 812.43; ISO 14155:2011 Section 8.2.1), monitoring (21 CFR 812.46; ISO 14155:2011 Section 8.2.4.2), supplemental applications (21 CFR 812.35 (a) and (b)), record maintenance (21 CFR 812.140 (b)), and report submissions (21 CFR 812.150 (b)).

11.1 General Duties

(21 CFR 812.40; ISO 14155:2011 Section 8)

The Sponsor's general duties consist of submitting the IDE application to FDA, submitting the Investigational Plan to other applicable national regulatory agencies (as applicable), obtaining FDA, other national regulatory (as applicable) and IRB / EC approvals prior to shipping the devices, selecting qualified Investigators, and shipping devices only to those qualified Investigators. As the sponsor, Veryan is also required to obtain signed study agreements, to provide the Investigators with the information necessary to conduct the study and adequate on-site training to conduct the trial, to ensure proper clinical site monitoring, and to provide the required reports to the Investigators, IRBs / ECs, other national regulatory agencies (as applicable), and FDA.

Veryan will be responsible for providing quality data that satisfies federal regulations and informing about serious unanticipated adverse events and deviations from the Protocol. Written progress reports and a final report will be prepared in coordination with the Ultrasound, Angiographic and X-Ray Core Laboratories.

11.2 Selection of Clinical Sites & Investigators

(21 CFR 812.43; ISO 14155:2011 Section 8.2.1)

Veryan will select qualified clinical sites and Investigators who are experienced with percutaneous transluminal angioplasty and peripheral stenting. The Investigator must work with a qualified IRB / EC to oversee the rights, safety and welfare of the study participants. The clinical site must also have an adequate subject population and the appropriate staffing and equipment to meet the requirements of the study Protocol and the expected enrollment time frames.

11.3 Monitoring

(21 CFR 812.46; ISO 14155:2011 Section 8.2.4.2)

Veryan will designate a CRO to monitor and oversee the conduct of the MIMICS-2 study. The Sponsor and/or CRO designee will conduct investigational site monitoring to ensure that all Investigators are in compliance with the Protocol and the Investigators' agreements. The Sponsor and/or CRO designee will monitor the sites to ensure that the completed eCRFs are in agreement with the source documentation and other records, and resolve any differences. Periodic phone contacts and site visits will be conducted to ensure that the Protocol is being followed.

For record verification purposes, the clinical monitor and/or authorized Sponsor representative will be provided access to hospital records, original laboratory data, and other records and data as they relate to the study and as agreed to with the Investigator prior to the initiation of the trial. The Investigator will also make available to the clinical monitor all regulatory documents, all completed eCRFs, informed consent documents, source documentation and other relevant records for all

enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitor during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If the Sponsor and/or their authorized representative become aware that an Investigator is not complying with the study Protocol, the Investigator Agreement, the Declaration of Helsinki, applicable privacy standards, or any condition of the study imposed by the IRB / EC, the Sponsor or their authorized representative may immediately secure compliance or discontinue further shipments of the study devices. An inability to secure compliance and/or to complete an investigation into the factors that are inhibiting compliance may result in the Investigator's termination from the study by the Sponsor.

The Sponsor will review significant new information, including unanticipated serious adverse events and ensure that such information is provided to the FDA, other national regulatory agencies (as applicable), the Investigators, and to all reviewing IRBs / ECs.

Study close-out visits will be conducted after the final follow-up visit is completed at each site following the resolution of any outstanding data discrepancies and adverse events. The remaining study devices will be the collected and returned to the Sponsor on or before the close out visit. A final study report will be generated and submitted to the Investigator and the appropriate study oversight authorities. Study document retention requirements will be reviewed with each site during the close-out visit.

11.3.1 Investigational Site Termination

The Sponsor reserves the right to terminate an investigational site from the Study for any of the following reasons:

- Failure to obtain Informed Consent.
- Failure to report Serious Adverse Events within 48 hours of knowledge.
- Loss of or unaccountable device inventory.
- Repeated Protocol violations or safety concerns.
- Repeated failure to complete Case Report Forms.
- Failure to enroll an adequate number of subjects.

11.4 Informed Consent & Institutional Review Board / Ethics Committee

(21 CFR Parts 50 & 56; ISO 14155:2011 Section 4)

All subjects must provide written informed consent in accordance with the local clinical site's IRB / EC. A copy of the consent form from each center must be forwarded to the Sponsor for review and approval prior to submitting it to the IRB / EC. Each site must provide the Sponsor with a copy of the clinical site's IRB / EC approval letter and the informed consent. Continuing review (e.g., institutional annual review) approvals for the continuation of the trial at each clinical site must also be forwarded to the Sponsor, as applicable.

All Protected Health Information (PHI) to be collected in the study will be described in the informed consent form, and all study data will be managed in accordance with the Privacy Law (HIPAA) or international privacy regulations, as applicable.

11.5 Records & Record Retention

(21 CFR 812.140 (b) & (d))

The Sponsor and/or their designated CRO will maintain copies of correspondence, data, device shipments, clinical events (AEs, SAEs, MAEs) and supporting documentation and other records and reports related to this clinical study.

The Sponsor, core laboratories and clinical sites will maintain the MIMICS-2 study records until two (2) years after the final study report is completed, or longer if required by local, national or international regulatory agencies. The Sponsor will notify each site regarding the regulatory requirements for record retention during the study close-out visit.

11.6 Study Reports

(21 CFR 812.150 (b))

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

The Sponsor will submit the required FDA reports identified in this section of the regulation. This includes unanticipated serious adverse device effects, withdrawal of IRB / EC or FDA approval, current 6-month Investigators list, annual progress reports, recall information, final reports, investigators that use the device without obtaining informed consent, and significant risk device determinations.

Upon receipt of the final study data and the final reports from each center, the Sponsor will complete a final study report. Copies of the final report will be provided to each Investigator.

11.7 Supplemental Applications

(21 CFR 812.35)

As appropriate, the Sponsor will submit changes to the study Protocol for national approval and subsequently to the Investigators to obtain IRB / EC approval.

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12.0 QUALITY ASSURANCE & ETHICAL STANDARDS

The study will be conducted according to the Declaration of Helsinki, GCPs, 21 CFR parts 50, 54, 56 and 812, ISO 14155:2011, and any additional IRB / EC, local (site and/or state requirements) and/or national requirements that apply to clinical studies of medical devices. As the study Sponsor, Veryan, has the overall responsibility for the conduct of the study, including the assurance that the study is in compliance with these guidelines, standards and requirements.

12.1 Institutional Review Boards / Ethics Committees

A copy of the study Protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB / EC for written approval. A copy of the written IRB / EC approval of the Protocol and Informed Consent form must be received by Veryan before recruitment of subjects into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB / EC as well as the FDA, for all subsequent significant Protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the IRB / EC of deviations from the Protocol or SAEs and UADEs occurring at the site and other SAE/UADE reports received from Veryan in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB / EC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB / EC continuance of approval must be sent to Veryan.

12.2 Informed Consent

A sample Informed Consent form template shall be provided to the Investigator to use to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population.

The reviewing IRB / EC and the sponsor must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the FDA Regulations, GCP guidelines, Declaration of Helsinki, and ISO Standards.

Prior to participation in the clinical trial, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to read the consent, ask questions, and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the subject's, or their legal representative's dated signature. The subject will receive a copy of the Informed Consent form.

12.3 Protocol Amendments

An Investigator may not make changes to this Protocol without prior approval by the Sponsor. All significant changes to the Protocol that may affect the following must be submitted and approved by the FDA before initiating the change:

- Validity of the data or information resulting from the completion of the approved Protocol.
- Relationship of the likely subject risk to benefit relied upon to approve the Protocol.
- Scientific soundness of the investigational plan.
- Rights, safety, or welfare of the human subjects involved in the investigation.

Any such change to the Protocol must be approved by the FDA and submitted and subsequently approved by the site IRB / EC. Veryan will submit a copy of the Protocol amendment to all Investigators for their IRBs / ECs to review and ensure the study continues to be conducted consistently across all

sites. The investigative sites must send Veryan a copy of the IRB / EC approval letter for the Protocol amendment.

Veryan may make certain administrative changes to the Protocol without prior approval of the FDA or IRB / EC. Veryan will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites. The site IRBs / ECs will be notified of these changes.

12.4 Emergency Actions

Veryan accepts the right of the Investigator to deviate from the Protocol in an emergency when necessary to safeguard the life or the physical well-being of a study subject. The Investigator must give notice of any emergency deviations and justification for the deviation to Veryan and the IRB / EC as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

Emergency Use of the investigational device is not permitted in this study.

12.5 Protocol Compliance

A Protocol deviation is defined as an event where the Clinical Investigator or site personnel did not conduct the study according to the Protocol.

Investigators shall be required to obtain prior approval from the Sponsor's clinical study management before initiating deviations from the Protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate eCRF.

Deviations must be reported to the Sponsor regardless of whether medically justifiable, pre-approved by the Sponsor or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation case report form. Non-subject specific deviations, (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to the Sponsor reported via the applicable site monitoring visit report. Investigators will also adhere to procedures for reporting study deviations to their IRB / EC in accordance with their specific IRB / EC reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the Protocol. For reporting purposes, the Sponsor classifies study deviations as major and minor:

> *Major deviation*: Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures, SAE/MAE reporting, device accountability discrepancies, or unauthorized device use.
>
> *Minor deviation*: Deviation from a Protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc. Minor Deviations that continue to occur at an investigational site may be classified as Major Deviations if corrective action is not taken to secure future compliance to the Protocol.

12.6 Investigator & Staff Training

Training of the Investigators and clinical study staff is the responsibility of the Sponsor and their designee. Training may be conducted during an Investigator meeting, a site initiation visit, or appropriate training venues. Investigators and study staff will undergo training on the study devices

and study Protocol, eligibility criteria, device accountability, and proper storage of the equipment and supplies, prior to participating in the study. Training may encompass didactic information regarding the study devices and system, as well as hands-on practice with the device. Procedural technique and experience with the BioMimics 3D Stent System may be assessed by clinical/engineering personnel. Observations during the cases will also be discussed with the Investigator and study staff.

12.7 Audits and Inspections

The Principal Investigator for the site will also allow representatives of the governing IRB or EC, the United States Food and Drug Administration (FDA), and other applicable regulatory agencies to inspect all trial records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the trial. These inspections are for the purpose of verifying adherence to the Protocol, completeness and exactness of the data being transcribed into the eCRF, and compliance with FDA or other regulatory agency regulations.

The Principal Investigator for the site will inform the Sponsor or the Sponsor's designee in advance if they are to be audited or inspected by any regulatory agencies. The Sponsor or the Sponsor's designee will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

The Investigator and/or designees must be available to respond to reasonable requests by authorized Sponsor, CRO and regulatory agency representatives during the monitoring and inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (i.e., Inspection Observations) or their qualification as an Investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits, if any.

12.8 Monitoring Procedures

12.8.1 Monitoring

Monitoring visits to the clinical sites will be made periodically during the study, to ensure that all aspects of the current, approved Protocol/amendment(s) are followed. Original source documents shall be reviewed for verification of data in the electronic database according to the defined monitoring plan. The Investigator/institution shall make all attempts to grant direct access to original source documents by Veryan personnel, their designees, and appropriate regulatory authorities. It is recognized that all participating institutions may not have procedures for providing access to electronic health records to non-institutional employees. In such situations, the Sponsor and/or designee shall collaborate with the investigator and institution to ensure alternative access to the complete medical record for enrolled subjects. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review.

Site visits will be conducted to ensure that the Protocol is being followed and that any Protocol deviations are properly documented. Additionally, telephone and/or e-mail contact will be conducted on a regular basis with the investigator and the site staff to ensure that the Protocol is being followed and to address any issues that may occur during the course of the trial. Clinical monitoring will include a verification that Informed Consent was properly obtained for all enrolled trial participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents. The clinical monitor will verify that the eCRFs are in agreement with the source documentation and other records. The investigator will make available to the clinical monitor for review all Informed Consent documents, Internet access to completed eCRFs, source documentation, original laboratory data and other relevant records for all enrolled subjects at the site. It is important that the investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If a deficiency is noted during an on-site visit (or at any other time during the course of the trial), the clinical monitor is required to discuss the situation with the investigator and the Sponsor (if required) to secure compliance.

12.9 Investigational Device Distribution and Accountability

12.9.1 Investigational Device Distribution

Veryan will control the distribution of the investigational devices. Each investigational site will be responsible for ordering the investigational devices for the study. The Investigator is responsible for ensuring that the devices are ordered for shipment to arrive at the hospital before the procedure date. Devices will be shipped with an Investigational Device Shipment Record. This form is to be used by Veryan, or distribution designee, and the investigational site to record any shipments of the investigational device. A copy is to be retained by the shipper and the recipient.

12.9.2 Device Accountability

The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision and are only used according to this Protocol and any approved amendments. The Investigator will not supply an investigational device to any person not authorized to participate in the MIMICS-2 Study. The Investigator shall document in the operative notes and eCRFs the lot/device numbers of the devices used during an index procedure. In addition, the Investigator shall keep complete and accurate records of all devices used or unused that have been returned to the Sponsor in a Device Accountability Log provided by Veryan.

12.9.3 Return of Study Materials at Study Termination / Completion

After enrollment is completed, all unused devices must be accounted for and shipped back to the Sponsor. Instructions for device return to the Sponsor will be reviewed at the site initiation visit as well as following study enrollment closure.

IMPORTANT: Please note that the devices must be labeled with a "BIOHAZARD" sticker if there is reasonable belief that the device has come in contact with blood or infectious substances that are known or are believed to cause disease in animals or humans.

12.10 Clinical Events Committee

An independent Clinical Events Committee (CEC) will be responsible for systematic review and adjudication of all major adverse events including death, and all potentially device- or procedure-related adverse events. In the case of an MAE with associated imaging, the CEC may review imaging assessments to assess the reported event.

At a minimum, the CEC shall consist of at least three (3) independent physicians, with experience in interventional peripheral endovascular procedures.

In order to enhance objectivity and reduce the potential for bias, the CEC members shall be independent of the Sponsor as well as the investigational sites and investigators. The methodology for performing these responsibilities shall be developed and outlined in the Safety Charter. Operational provisions shall be established to minimize potential bias.

12.11 Data Management

Standardized eCRFs will be utilized by all participating sites. Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered into eCRFs via a secure, web-based system with password protection. Incoming data will be automatically reviewed to identify inconsistent or missing data and any adverse events.

Any data issues are to be promptly addressed with the investigator by the CRO, the Sponsor designee and/or data manager. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that Protocol requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigators are to maintain all source documents as required by the Protocol, including laboratory results, supporting medical records, and signed Informed Consent forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed eCRFs.

The Investigator must maintain detailed records on all subjects who sign the Informed Consent and begin the pre-procedure evaluation. Only subjects who are enrolled and treatment is attempted or completed will have data entered into the eCRFs provided by the Sponsor. All data should be entered completely and promptly. For source documents, corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change, along with the reason for the change (if not obvious).

Study Exit eCRFs are completed for all enrolled and treated subjects, regardless if they did or did not complete the trial (e.g., subject discontinuation, trial termination).

12.12 Central Core Labs – Angiography, Duplex Ultrasound, X-Ray

In order to ensure that the clinical data and images are analyzed in a controlled, non-biased manner and that the results are analyzed using a standardized process, all angiograms, duplex ultrasound studies and X-rays obtained during this study per study requirements will be submitted to central core labs for analysis.

The core labs will be responsible for analyzing the angiograms and ultrasound images according to the study eligibility criteria, the study endpoints and this study Protocol. In addition, they will provide feedback to the sites and Sponsor regarding the quality of the tracings and images. The X-ray core lab will be assessing for stent fracture at the applicable study time points. Final written summary reports of all angiograms, X-rays, and duplex ultrasounds will be provided to the study Sponsor.

12.13 Subject Compensation

The treated subjects will not be reimbursed or compensated for participating in the trial. Travel expenses may be reimbursed by the Sponsor subject to approval by Sponsor and/or IRB/EC.

12.14 Confidentiality

Confidentiality of subjects will be maintained throughout the MIMICS-2 Study. A unique identification code will be assigned to each subject participating in this trial. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor and their representatives will make every reasonable effort to protect the confidentiality of the subjects participating in the MIMICS-2 Study.

13.0 STUDY DEFINITIONS

Access Site Hemorrhage: Bleeding from the access site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management. Hemorrhage needing ≥ 1 unit RBCs will be considered a serious adverse event.

Access Site Infection: Culture-proven wound infection or presumptive treatment with antibiotics for clinically diagnosed wound infection.

Acute Renal Failure: Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of > 1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is > 2.0 mg/dl; (b) a new requirement for dialysis.

Allergic Reaction: An allergic reaction characterized by rash, upper respiratory congestion, urticaria, shortness-of-breath, or general collapse (anaphylaxis).

Amputation:

Major: any requirement for amputation of the target limb above the ankle.
Minor: any requirement for amputation of the of the target limb below the ankle.

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to below 26%. Any documented anemic event requiring ≥2 units PRBCs will be considered an SAE.

Angina, unstable: Angina that increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset. Unstable angina is a syndrome that is intermediate between stable angina and myocardial infarction: it is characterized by an accelerating or "crescendo" pattern of chest pain that lasts longer than stable angina, occurs at rest or with less exertion than stable angina, or is less responsive to medication. Unstable angina and myocardial infarction are considered acute coronary syndromes.

Ankle Brachial Index (ABI): The ratio of systolic blood pressure measured at the ankle to systolic blood pressure measured at the brachial artery. It is used to predict the severity of peripheral arterial disease (PAD). ABIs >0.9-1.2 = normal, ≤ 0.9 = peripheral arterial disease, < 0.4 = severe peripheral arterial disease (ischemic pain and ulceration). ABI > 1.2 is likely due to incompressible arteries and is commonly observed in association with long-standing diabetes mellitus, extreme old age, or calcinosis.

Instructions for ABI Calculations:

1. Obtain systolic blood pressures (SBP) for both arms (brachials) and both ankles [posterior tibials (PT) & dorsalis pedals (DP)].
2. Divide the higher of the two SBPs for each leg (highest between the PT and DP) by the higher of the two arm pressures to get the right and left ABIs.

Arterial Occlusion / Thrombosis at Groin Puncture Site: Angiographic or ultrasonographic evidence of occlusion at the puncture site limiting antegrade flow to the distal limb.

Arterial Perforation/Rupture/Puncture of an Arterial Wall: Classified as follows:

Angiographic perforation: Perforation detected by the clinical site at any point during the procedure.
Clinical perforation: Perforation requiring additional treatment (including efforts to seal the perforation), or resulting in significant extravasation of blood from the site, abrupt closure, limb ischemia or death.

Arterial Pseudoaneurysm: Disruption of arterial wall confirmed by imaging study and requiring intervention.

Arteriovenous Fistula (AVF): An abnormal passage or communication between an artery and a vein which may be due to the percutaneous introduction of ancillary devices (e.g., needles, catheters, guide wires) confirmed by imaging studies.

Bleeding Complication (Major): Bleeding resulting in ≥3 g/dl decrease in hemoglobin (if hemoglobin level not available, a decrease in hematocrit of ≥ 10%), or necessitating transfusion of >1 unit of PRBC's /whole blood, or necessitates surgery/endoscopic intervention.

Access site: Bleeding from the arteriotomy site which requires transfusion, hospitalization (either admission or extended stay), or further treatment for management.

Cardiac Arrhythmia: Electrical disruption of the heart rhythm requiring specific medication, DC shock, or pacemaker insertion to address condition.

Cardiogenic Shock: Subject presents with SBP < 80 mm Hg for more than 30 minutes unresponsive to fluids or requiring intravenous vasopressor agent or an intra-aortic balloon pump (IABP).

Cerebral Vascular Accident (CVA): See Stroke.

Classification of Calcification: Intimal and medial vessel wall calcification at the target lesion site as assessed by high intensity fluoroscopy and digital subtraction angiography (DSA) assessed in the AP projection [41].

Peripheral Arterial Calcium Scoring System (PACSS):

Grade 0: No visible calcium at the target lesion site.
Grade 1: Unilateral calcification <5cm: a) intimal calcification; b) medial calcification; c) mixed type.
Grade 2: Unilateral calcification ≥5cm: a) intimal calcification; b) medial calcification; c) mixed type.
Grade 3: Bilateral calcification <5cm: a) intimal calcification; b) medial calcification; c) mixed type.
Grade 4: Bilateral calcification ≥5cm: a) intimal calcification; b) medial calcification; c) mixed type.

Classification of Lesion Morphology (TASC II) [42]

TASC II type A lesions:

- Single stenosis ≤ 10 cm in length
- Single occlusion ≤ 5 cm in length

TASC II type B lesions:

- Multiple lesions (stenosis or occlusions), each ≤ 5 cm
- Single stenosis or occlusion ≤ 15 cm not involving the infrageniculate popliteal artery
- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
- Heavily calcified occlusions ≤ 5 cm in length
- Single popliteal stenosis

TASC II type C lesions:

- Multiple stenosis or occlusions totaling > 15 cm, with or without heavy calcification
- Recurrent stenosis or occlusions that need treatment after two endovascular interventions

TASC II type D lesions:

- Chronic total occlusion of the common or superficial femoral arteries (> 20 cm, involving the popliteal artery)
- Chronic total occlusion of the popliteal artery and proximal trifurcation vessels

Closure, Abrupt: Occurrence of new (during the index procedure), persistent slow, reduced, or loss of flow within the target vessel that requires intervention other than the index or adjunct treatment. Abrupt closure may also be referred to as acute occlusion if there is a total loss of flow.

Closure, Late: Target lesion site occlusion that occurs greater than 30 days after the index procedure is completed (e.g., the subject has left the treatment area).

Closure, Subacute: Target lesion site occlusion that occurs after the index procedure is completed (e.g., the subject has left the treatment area) and within 30 days of procedure.

Contrast-Induced Nephropathy: Associated with contrast agent resulting in > 25% increase in serum creatinine or an absolute value of > 0.5 mg/dl.

Contrast Media Reaction: An allergic reaction, immediate or delayed, associated with the intravascular administration of contrast media that results in symptoms (e.g. itching, hives) or physiologic changes requiring treatment (e.g. anaphylactic reaction) or death.

Critical Limb Ischemia (CLI): Clinical manifestation of peripheral arterial disease characterized by Rutherford Clinical Scale Category of 4-6. For the purposes of this study, only subjects with Rutherford Clinical Scale Category of 2, 3, and 4, are eligible for enrollment.

Death: Death is divided into 2 categories:

Cardiovascular death is defined as death due to any of the following:

1. Acute myocardial infarction.
2. Sudden cardiac death.
3. Death due to heart failure.
4. Death due to stroke.
5. Death due to other cardiovascular causes.
6. Death not attributable to any other cause (e.g., undetermined cause of death).

Non-cardiovascular death is defined as a death not due to cardiovascular causes (as listed above).

Deep Vein Thrombosis (DVT): Thrombosis of a deep vein, as confirmed by imaging study or direct visualization.

Femoropopliteal: DVT involvement limited to the superficial femoral or popliteal veins, with or without distal (e.g. toward foot) DVT involvement, based on duplex ultrasound exam.
Iliofemoral: DVT involvement of the common or external iliac veins or the common femoral vein, with or without distal (e.g. toward foot) DVT involvement, based on duplex ultrasound exam.

De Novo Lesion: An obstructive or occlusive lesion without previous endovascular or surgical intervention

Device Failure: A device that is used in accordance with the Instructions for Use, but does not perform according to the Instructions for Use and negatively impacts the treatment.

Device Malfunction: A malfunction of a device is an unexpected change to the device that is contradictory to the Instructions for Use and may or may not affect device performance.

Dissection: Disruption of an arterial wall resulting in separation of the intimal layer. May or may not be flow limiting.

Dissection Classifications (National Heart, Lung and Blood Institute – NHLBI)

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 our 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 coronary occlusion.

Embolization, Distal: Any distal emboli confirmed by imaging.

Embolization, Symptomatic: Clinical signs or symptoms of distal emboli detected in the treated limb distal to the treated lesion after the index procedure ***or*** noted angiographically and requiring mechanical or pharmacologic means to improve flow. This includes new abrupt occlusions or filling defects.

Enrollment: Subjects who are consented and meet all the study inclusion criteria and none of the study exclusion criteria and are treated or treatment is attempted with the study device will be considered enrolled into the study. Subjects who do not meet all inclusion and exclusion criteria (e.g., including ability to cross the lesion with a guidewire, target reference vessel diameter, target lesion length, calcification exclusion, patent popliteal and tibioperoneal artery in the target limb, etc.) will be considered an angiographic screen failure and will not be followed in the study (no data will be collected on these subjects).

Hematoma: Collection of blood (or its degradation products) which exceeds 5 cm in diameter, requires treatment, or prolongs hospitalization.

Hypertension: Systolic BP >140 mmHg, or diastolic >90 mmHg requiring specific medical therapy.

Hypotension: Any prolonged systolic blood pressure <80 mmHg associated with symptoms and requiring intravenous vasopressor medications.

Infection, access site: Infection at the vascular access site, documented by lab culture or clinical evidence requiring medical treatment (irrigation, debridement, antibiotics, etc.) to resolve.

Infection, systemic: Systemic infection documented by positive lab culture or clinical evidence, requiring medical treatment to treat and resolve.

Intention to Treat (ITT): The principle of including outcomes of all subjects in the analysis who are enrolled and treated (attempted or completed) into the study, regardless of noncompliance, Protocol deviations, or withdrawal.

Limb Ischemia: Deficient supply of oxygenated blood to the tissues in the limbs that is due to obstruction of the inflow of arterial blood characterized by pain and/or discoloration of the limb and/or tissue loss.

Luminal Patency: Restenosis <50% as determined by angiography or duplex ultrasound.

Major Adverse Event (MAE): An MAE comprises all-cause death, any major amputation performed on the target limb or clinically-driven target lesion revascularization.

Myocardial Infarction (MI): Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Patency, Primary Stent: Patency is defined as no significant reduction in luminal diameter (i.e. < 50% diameter stenosis) since the index procedure. Luminal diameter is assessed by core lab using angiography or duplex ultrasound imaging. Loss of primary stent patency is deemed when peak systolic velocity ratio (PSVR) is >2.0, or where angiography reveals >50% diameter stenosis, or where the subject undergoes clinically-driven TLR. When both imaging modalities are available, angiography takes precedence.

[redacted]

Patency, Tibioperoneal Run-Off: Subject has at least one patent tibioperoneal run-off vessel with <50% stenosis confirmed by angiography at time of enrollment.

Perforation: Puncture of an arterial wall.

Pseudoaneurysm: Disruption of the arterial wall characterized by an out-pouching or pocket with swirling, flowing blood outside of the confines of the arterial lumen.

Recurrent Occlusion: Occlusion (i.e. total obstruction of vessel lumen) after a successful canalization.

Recurrent Thrombosis: Thrombosis (i.e. sub-total obstruction of vessel lumen) following successful treatment.

Reference Vessel Diameter, Proximal (RVD_{prox}): Diameter of normal vessel immediately proximal to the treated segment.

Reference Vessel Diameter, Distal (RVD_{dist}): Diameter of normal vessel immediately distal to the treated segment.

Renal Failure (Acute): Acute post-operative renal insufficiency resulting in one or more of the following: (a) increase of > 1.0 mg/dl in serum creatinine from most recent prior measured level, and current measured absolute value is > 2.0 mg/dl; (b) a new requirement for dialysis.

Renal Insufficiency: An increase in serum creatinine of ≥ 1.0 mg/dl over previous value requiring medical treatment but which does not require dialysis to resolve.

Respiratory Failure: New onset of respiratory insufficiency that requires placement of endotracheal tube and/or pneumothorax with or without chest tube.

Respiratory Insufficiency: Deterioration of subject's respiratory efforts that require supportive or medical treatment.

Restenosis: Reoccurrence of narrowing or blockage or target lesion. Recurrence of ≥ 50% diameter stenosis within ± 5 mm proximal and/or distal to the target lesion as measured by duplex ultrasound (PSV ≥ 2.0) or angiography (note: in cases where both imaging modalities are available, the angiography will take precedence).

Retroperitoneal Bleed: Bleeding into the back of the abdomen from a vascular access or puncture site.

[redacted]

Rutherford Clinical Category Scale: Clinical scale identifying three grades of claudication and three grades of critical limb ischemia ranging from rest pain alone to minor and major tissue loss [46].

Category	Clinical Description
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss
6	Ulceration or gangrene

Stent Fracture: Defined as clear interruption of stent strut observed in a minimum of two projections, determined by core lab examination of X-ray images.

Stent Strut Fracture Types: [26]**,** [47]

Type 0: No strut fractures.
Type I: Single strut fracture only.
Type II: Multiple single strut fractures that can occur at different sites.
Type III: Multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments.
Type IV: Multiple strut fractures resulting in displacement of segments of the stent.
Type V: Spiral strut fracture.

Stroke: Any neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction consistent with deficit. May be further categorized as:

- Ischemic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to thromboembolic event.
- Hemorrhagic Stroke: neurologic deficit meeting the study definition for Stroke that is attributed to bleeding into brain tissue, epidural, subdural, or subarachnoid space; or a combination of these sites.

Target Lesion Revascularization, Clinically-driven (CDTLR): Revascularization of the target lesion with objective evidence of recurrent symptoms associated with an angiographic determination of ≥50% stenosis and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the index limb); or ≥70% diameter stenosis in the absence of objective evidence of recurrent symptoms.

Target Vessel Revascularization, Clinically-driven (CDTVR): Revascularization of the target vessel with objective evidence of recurrent symptoms associated with an angiographic determination of ≥50% stenosis and new distal ischemic signs (worsening ABI or worsening Rutherford Category associated with the index limb); or ≥70% diameter stenosis in the absence of objective evidence of recurrent symptoms.

Thrombocytopenia: A persistent decrease in the number of blood platelets to subnormal levels.

Toe Brachial Index (TBI): A Toe Brachial Index (TBI) is performed when the ABI or Ankle Brachial Index is abnormally high due to plaque and calcification of the arteries in the leg; this is caused by atherosclerosis and is most often found in diabetic patients. The abnormally high ABI is >1.3.

Instructions for TBI Calculations:

1. Obtain systolic blood pressures (SBP) for both arms (brachials) and both great toes.
2. Divide the higher of the two SBPs for each leg (highest between the PT and DP) by the great toe pressure to get the right and left TBIs.

Thrombus: Blood clot that obstructs a blood vessel.

Transient Ischemic Attack: A neurological event where symptoms last for less than 24 hours, with no evident permanent functional impairment.

Walking Impairment Questionnaire (WIQ): A measure of subject-perceived walking performance for patients with PAD and/or intermittent claudication. This questionnaire estimates walking distance, walking speed, and stair climbing. Improvement is defined as an increase of walking distance

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APPENDIX A – CORE LABORATORIES

In order to ensure that the clinical data and images are analyzed in a controlled, non-biased manner and that the results are analyzed using a standardized process, all angiograms, duplex ultrasound, and X-ray studies obtained during this study will be submitted to a central core lab for analysis.

The core labs will be responsible for analyzing the angiograms, ultrasound, and X-ray images according to the study eligibility criteria, the study endpoints and this study Protocol, for providing feedback to the sites and Sponsor regarding the quality of the tracings and images and for providing a written summary report of all angiograms and duplex ultrasound results to the study Sponsor.