STATISTICAL ANALYSIS PLAN
MIMICS-2

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

Protocol Number:	CID-100 Issue 09
Name of Test Drug/Device:	BioMimics 3D^{TM} Stent System
Sponsor:	Veryan Medical Ltd
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Document Date:	25 April 2018
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Confidentiality Statement

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1.   SIGNATURE PAGE

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

Sponsor: Veryan Medical Ltd

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Protocol Number: CID-100 Issue 09

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2. STUDY SYNOPSIS

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 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. ██
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

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	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). 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.
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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)

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	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 <u>re-intervention</u> 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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3.   LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	Six-Minute Walk Test
ABI	Ankle Brachial Index
AE	Adverse Event
CDTLR	Clinically Driven Target Lesion Revascularization
CEC	Clinical Events Committee
CFR	Code of Federal Regulation
eCRF	electronic Case Report Form
EC	Executive Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ITT	Intent to Treat
IQR	Interquartile Range
IRB	Institutional Review Board
MAE	Major Adverse Event
mITT	modified Intent to Treat
NYHA	New York Heart Association
OPG	Objective Performance Goal
OUS	Outside United States
PAD	Peripheral Artery Disease
PMA	Premarket Approval
PTA	Percutaneous transluminal angioplasty
PSVR	Peak Systolic Velocity Ratio
PVD	Peripheral Vascular Disease
RVD	Reference Vessel Diameter
RCC	Rutherford Clinical Category
SAE	Serious Adverse Event
SAS	Statistical Analysis System
TBI	Toe Brachial Index
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
US	United States
VIVA	Vascular Interventional Advances
WIQ	Walking Impairment Questionnaire

Abbreviation	Definition
6MWT	Six-Minute Walk Test

4.   INTRODUCTION

The purpose of this statistical analysis plan is to provide additional details on the derivation of variables and statistical analyses to be performed for this study. The database will lock when the 12-month visit is completed for all patients. All planned analyses will be performed at this time. There will continue to be annual follow-up visits for the collection of relevant medications and adverse events for 2 additional years. Interim analyses will be conducted for annual progress reporting as described herein.

5.   STUDY OBJECTIVES

The objective of the study 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.

6.   INVESTIGATIONAL PLAN

6.1.   Overall Study Design and Plan

The MIMICS-2 Study is a prospective, single arm, multicenter trial 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. 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.

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.

6.1.1.   Choice of Control Groups

There is no concurrent control group in this study. Primary effectiveness and safety will be compared to the 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.

6.1.2.   Method of Assigning Patients to Treatment Groups

This is a single arm study.

6.2.   Study Endpoints

6.2.1.   Primary Safety Endpoints

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 Clinically Driven Target Lesion Revascularization (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.

6.2.2.   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.

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6.2.3.   Secondary Endpoints
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.[4]

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.

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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.

7.   DATA QUALITY ASSURANCE AND COMPUTING ENVIRONMENT

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.

Standardized electronic case report forms (eCRFs) will be used to collect complete and accurate records of the clinical data from the MIMICS-2 trial according to the GCP 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.

Statistical analyses will be performed using the SAS Software package [2,3].

8.   PATIENT POPULATIONS

8.1.   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. If no subjects are excluded, that is, if the ITT and mITT analysis sets contain the same subjects, then all mITT analyses will revert to the ITT analysis set and the mITT analysis set will be eliminated.

- *Per Protocol (PP) Analysis Set*: includes all mITT subjects who additionally met all inclusion/exclusion criteria. This is a secondary analysis set for the primary safety and effectiveness endpoints, as well as secondary 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 and PP analysis sets as supportive information. All subjects excluded from mITT and PP analysis sets will be described in the final study report and the reasons detailed. If the ITT and mITT analysis sets contain the same subjects, then all mITT analyses will revert to the ITT analysis set and the mITT analysis set will be eliminated.

8.2. Protocol Deviations

This study will be conducted as described in the protocol, except for an emergency situation in which the protection, safety, and well-being of the patient require immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). 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. Protocol deviations will be reported in tabular form (number of deviations and number of subjects with deviations) as well detailed in a listing.

9. STATISTICAL METHODS

9.1. Determination of 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).[4]

- 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, 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 [5] 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 [5]. 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█, or where angiography reveals >50% diameter stenosis, or where the subject undergoes clinically-driven TLR. When both imaging modalities are available, angiography takes precedence.

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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.

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Final sample size determination

In order to statistically power both of the primary endpoints simultaneously, 230 evaluable subjects at 12 months are required. It was initially determined that in order to allow for attrition, a sample size of 280 subjects should be enrolled in the MIMICS-2 Study; however, enrollment was stopped at 271 subjects with the expectation that greater than 230 subjects will be evaluable at 12 months based on current drop-out rates and updated estimates of availability of diagnostic DUS images. The power for the primary safety endpoint is actually >99%, keeping the overall study power at approximately 85%.

9.2.   General Considerations

9.2.1.   General Methods

All descriptive statistical analyses will be performed using SAS Version 9.4 or higher [2,3], unless otherwise noted.   Derived variables will be independently verified by an independent programmer/statistician. The program review also will include a check whether analyses conform to specifications of the Statistical Analysis Plan. All output will be incorporated into Microsoft Excel or Word files, and formatted as to the appropriate page size(s).

For categorical variables, the number and percentage within each category of the parameter will be calculated. For continuous variables, the N, median, IQR, mean, standard deviation, minimum and maximum values will be presented.

For each parameter, the baseline value will be defined as the last non-missing value collected at the time closest to but before the start of study drug/device administration.

All statistical tests will be performed at the two-sided, 0.05 significance level, unless otherwise noted. Listings of patient data will be created for all study parameters.

9.2.2.   Adjustments for Covariates

No adjustments for covariates are planned.

9.2.3.   Handling of Dropouts or 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 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.

9.2.4.   Interim Analyses and Data Monitoring

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). Additional analyses will be conducted for annual reporting purposes and when all data have been collected for the 24 and 36 month visits.

9.2.5. Multicenter Studies

Poolability of study subjects across investigational sites will be explored by comparing the primary outcome measure across sites. 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.

9.2.6. Multiple Comparisons/Multiplicity

There are two independent primary endpoints in this study. Both endpoints must be met in order to declare study success, thus no adjustment to alpha is necessary to account for multiple endpoints.

9.2.7. Examination of Subgroups

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 differences 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.

Primary endpoints will be additionally 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 5mm stent diameter versus >5mm stent diameter.

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

The results of all subgroup analyses will be presented in the final study report regardless of the findings. 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.

9.2.8.   Analysis Windows and Definitions

Study subjects are 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. For ascertainment of the primary endpoints, if the subject is known to be event free at at least the lower limit of the visit window, that subject will be considered event free for the analysis. Thus, if a subject misses the 30 day visit, but is determined to have been event free up to the 12 month visit, then that subject will be considered event free. If the subject has no data past the lower boundary of the visit window, their data will be considered missing.

For the purposes of these analyses, 12 months is defined as 365 days post procedure, and similarly 24 and 36 months are defined as 730 and 1095 days, respectively. Procedure is considered day 0 so that days from procedure is defined as (visit date – procedure date).

9.3.   Patient Disposition, Demographics and Other Baseline Characteristics

A tabulation of patient disposition will be presented including number enrolled, number treated, and number of withdrawals, including reasons for withdrawal as documented on the case report form.

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 and PP analysis sets.

9.4.   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.

9.4.1.   Primary safety endpoint:

The primary outcome measure for safety is the composite of MAE as adjudicated by the CEC including death, major amputation performed on the target limb or CDTLR through 30 days from procedure. 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. [4]. 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 9.2.3 above.

9.4.2.   Primary effectiveness endpoint:

The primary outcome measure for effectiveness is primary stent patency rate at 12 months as defined in Section 6.2.2. 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.[4]. 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 qualifying as a 12 month visit and/or subjects without imaging data who experienced a CDTLR through 12 months (365 days). Additionally, if a subject is missing stent patency status at the 12 month visit window 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 9.2.3 above.

Both primary endpoints must be met in order to declare trial success.

9.5.   Secondary Endpoint Analyses

All secondary endpoints as described in Section 6.2.3 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.

9.5.1.   Secondary Endpoints

The following endpoints will be summarized as noted above:

- Contribution of individual MAE rates for death, major amputation performed on the target limb and CDTLR to the overall MAE rate at 30 days.

- Long-term safety assessment – overall MAE rate at Month 12 and contribution of individual event rates to the overall MAE. Freedom from MAE will be additionally displayed via Kaplan-Meier plots.

- Overall rate and incidence of type of serious adverse events from Day 0 through completion of Study follow-up at Month 36.

- 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.

- 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. ▌

- 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.

- Clinical outcome: comparison of Six-Minute Walk Test measured at Baseline, Day 30, Months 12 and 24 (sub-group of investigational sites).

- Functional outcome: comparison of the ankle brachial index (ABI) measurement at Baseline, within 30 days after index procedure, then at Months 12 and 24.

- 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.

9.5.2. Walking Impairment Questionnaire

In addition to the individual scores, the following summary scores will be calculated. If more than half of the components of the score are missing, the score is considered missing. [6]

- Walking distance score = (20 * (points for walking indoors)) + (50 * (points for walking 50 feet)) + (150 * (points for walking 150 feet)) + (300 * (points for walking 300 feet)) + (600 * (points for walking 600 feet)) + (900 * (points for walking 900 feet)) + (1500 * (points for walking 1500 feet)) / total possible score.

- Walking speed score = (1.5 * (points for walking slowly)) + (2 * (points for walking at average speed)) + (3 * (points for walking quickly)) + (5 * (points for running or jogging)) / total possible score.

- Stair climbing score = (1 * (points for climbing one flight of stairs)) + (2 * (points for climbing two flight of stairs)) + (3 * (points for climbing three flight of stairs)) / total possible score.

- Overall score is the average of the three scores above. If any score is missing, the overall score is missing.

9.7. Safety Analyses

9.7.1. Adverse Experiences

All adverse events collected will be coded according to the study coding manual. Events will be summarized cumulatively through the following time points: in-hospital, 30 days, 12 months, 24 months and 36 months.

Frequency count of Adverse Events and unique number of patients who had the AEs, for each coded term, will be presented. Also, the frequency and percentage of patients who had a Serious AE (SAE), or a related AE (by relationship to both procedure and device) will be tabulated separately by coded term.

If a patient experienced multiple AEs, only the most severe event or the most intense relationship to treatment will be counted within a particular AE code.

CEC adjudicated events will be tabulated.

9.7.2. Device Failures, Malfunctions

The number of device failures and malfunctions will be tabulated and included in a listing.

9.7.3. Concomitant Medications

Medication use will be summarized by at each study time point.

9.8. Post-Approval Study (36 Months)

9.8.1. Continued Follow-up of Pivotal Cohort

The MIMICS-2 IDE Study was designed as a 3-year follow-up study and will continue to assess subjects through completion of the 36-month visit, with the last subject due to exit the Study no later than Dec-2019. The follow-up assessments to be conducted at 36 months are outlined in the study protocol, CID 100 Issue 09 and these long-term follow-up data and conclusions will be reported within the final Clinical Study Report.

9.8.2. Primary Endpoint for Post-Approval Study

In addition to the previously specified MIMICS-2 IDE Study endpoints, a new 36-month primary endpoint is now defined as the rate of freedom from clinically driven target lesion revascularization (CDTLR), with clinical events adjudicated by the CEC. The 3-year rate of freedom from CDTLR will be estimated via Kaplan-Meier methods and presented along with the two-sided 95% confidence interval with error estimated via the Greenwood variance formula. Kaplan-Meier plots of CDTLR over time from Day 0 through Month 36 will be displayed.

10.   CHANGES TO ANALYSES PLANNED IN THE PROTOCOL

The primary endpoint for the post-approval study has been defined as the rate of freedom from CDTLR at 36 months, as documented in Section 9.8 of this document.

11.   REFERENCES

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2. SAS Institute Inc. (1999). SAS OnlineDoc, Version 8. SAS Institute Inc., Cary, NC, http://v8doc.sas.com/sashtml/.
3. SAS Institute Inc. (1999). SAS/STAT User's Guide, Version 8. SAS Institute Inc., Cary, NC.
4. K. Rocha-Singh, M. Jaff, T. R. Crabtree, D. A. Bloch, and G. Ansel, 'Performance Goals and Endpoint Assessments for Clinical Trials of Femoropopliteal Bare Nitinol Stents in Patients With Symptomatic Peripheral Arterial Disease', *Catheter. Cariovascular Interv.*, vol. 69, pp. 910–919, 2007.
5. Agresti and B. A. Coull, 'Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions', *Am. Stat.*, vol. 52, no. 2, p. 119, May 1998.
6. *Regensteiner JG Steiner JF et al. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. J Vascular Medicine Biology. 1990; 2: 142-152. (Appendix I pages 150- 151).*

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