Protocol Title:

# A Clinical Evaluation of the MicroSTent® PeripherAl Vascular SteNt in Subjects with Arterial Disease Below the Knee (STAND)

NCT: 03477604

SAP version date: 23DEC2025

[redacted]



# Micro Medical Solutions, Inc.

# A Clinical Evaluation of the MicroSTent® PeripherAl Vascular SteNt in Subjects with Arterial Disease Below the Knee (STAND)

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## Statistical Analysis Plan

[redacted] 23 DEC 2025

## Version History

[redacted]

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# 1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under [redacted], Clinical Investigation Protocol "A Clinical Evaluation of the MicroStent® Peripheral Vascular Stent in Subjects with Arterial Disease Below the Knee (STAND)".

This revised SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Investigation Protocol "A Clinical Evaluation of the MicroStent® Peripheral Vascular Stent in Subjects with Arterial Disease Below the Knee (STAND)" [redacted] Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

The following revisions are being made to this document after FDA's initial 12 June 2025 feedback of the clinical study report (CSR) that was submitted in December 2024:

[redacted]

# 2 Abbreviations

| *Abbreviation/Term* | *Definition* |
|---|---|
| ABI | Ankle brachial index |
| AE | Adverse event |
| AT | As treated |
| BDRM | Biostatistics Data Review Meeting |
| BMI | Body mass index |
| BTK | Below the knee |
| CAD | Coronary artery disease |
| CD-TLR | Clinically-driven target lesion reintervention |
| CD-TVR | Clinically-driven target vessel reintervention |
| CEC | Clinical Events Committee |
| CLI | Critical limb ischemia |
| CRF | Case report form |

| | |
|---|---|
| CSR | Clinical study report |
| DAPT | Dual antiplatelet therapy |
| DSMB | Data and Safety Monitoring Board |
| DUS | Duplex ultrasound |
| EDC | Electronic data capture |
| MALE | Major adverse limb event |
| mITT | Modified intent-to-treat |
| POD | Perioperative death |
| PP | Per protocol |
| PSVR | Peak systolic velocity ratio |
| PTA | Percutaneous transluminal angioplasty |
| RVD | Reference vessel diameter |
| SADE | Serious adverse device effect |
| SAP | Statistical analysis plan |
| SAE | Serious adverse event |
| SVS | Society of Vascular Surgery |
| TBI | Toe brachial index |
| TLMR | Target limb reintervention |
| TLR | Target lesion reintervention |
| TVR | Target vessel reintervention |
| UADE | Unanticipated adverse device effect |
| WIQ | Walking Impairment Questionnaire |

# 3 Study Objectives

Effectiveness

Demonstrate treatment with the MicroStent® System is superior to PTA alone in freedom from:

- Bail-out procedure
- Target lesion occlusion treated with clinically driven target lesion reintervention (CD-TLR). and
- Target limb major amputation

through 6 months of follow-up.

Safety

Demonstrate treatment with the MicroStent® System is non-inferior to PTA alone in freedom from: a) perioperative death, and b) major adverse limb events (MALE) through 6 months of follow-up.

# 4 Study Design

The study is a randomized multicenter clinical trial consisting of two arms; one arm treated with PTA plus the MicroStent® System and one arm treated with PTA alone. The MicroStent® System

(investigational device) (MicroStent) results will be compared to the control arm (standard PTA) to assess the safety and effectiveness of using a self-expanding bare metal stent for the treatment of infrapopliteal lesions in subjects with critical limb ischemia.

A core lab will be used for the angiography and ultrasound images. Wound healing will be assessed by use of a wound camera that calculates wound surface area. The assessments from the wound camera are confirmed by a medical expert in wound healing.

## 4.1 Randomization

Subjects will be randomized after all angiographic eligibility criteria have been confirmed and the guidewire has successfully crossed the target lesion. The subject will be considered enrolled in the study upon randomization.

Randomization will be performed using a random permuted block design stratified by investigational site with a 2:1 allocation ratio (PTA plus MicroStent: PTA only). Randomized treatment will be assigned within the study electronic data capture (EDC) system. Emergency envelopes will also be created using a schedule separate from the electronic randomization schedule. These envelope randomization assignments will only be used in emergency scenarios when the EDC system is inaccessible or inoperable or when the randomization module cannot be accessed.

## 4.2 Blinding

Blinding of subjects, investigators, ultrasound technicians and core lab personnel evaluating ultrasound images is impossible and is not a feature of this clinical trial. Subjects treated with the MicroStent® will be given an identification card used to alert health care providers that they have an implanted metal device. Investigators who perform the procedure will know which subjects received which treatment. Ultrasound technicians and core lab personnel will be able to visualize the MicroStent® (or absence of the stent) on angiographic and ultrasound images due to the radiopacity of the MicroStent.

## 4.3 Information Sources

The study will rely on multiple sources of information as follows.

| Determination | Source | Timepoint |
|---|---|---|
| Target Lesion occlusion | Ultrasound Core lab | All follow-up timepoints |
| Other Target Limb occlusion(s) | Ultrasound Core lab | All follow-up timepoints |
| Event relatedness | CEC | All follow-up timepoints |
| Clinically Driven TLR | CEC | All follow-up timepoints |
| MALE | CEC | All follow-up timepoints |
| Bailout procedure | CEC | Index procedure |
| Ischemic BTK Wound (Ulcers) Healing | Wound camera & Medical Expert | All follow-up timepoints |

## 4.4 Bias Control

The primary effectiveness endpoint is a composite that includes an objective ultrasound determination of target lesion occlusion. Ultrasound measurements and determination of occlusion will be made by an independent core lab. Clinical procedures qualifying as an endpoint event will be independently adjudicated by the CEC to determine the appropriateness of the intervention and the involvement of the target lesion. The biostatistician will not perform any effectiveness or safety analyses prior to database lock.

# 5 Sample Size Determination

The sample size calculations were conducted using nQuery 4.0. A 2 to 1 randomization scheme will be used for this study in which 2 subjects will be randomized to the MicroStent® arm for each subject randomized to PTA. Both the primary effectiveness and primary safety endpoint were considered. The final sample size was driven by the requirement for the primary effectiveness endpoint; see Section 5.1 for the primary effectiveness endpoint power for a superiority test and see Section 5.2 for the primary safety endpoint power for a non-inferiority test. The planned enrollment was 117 MicroStent® System and 60 PTA subjects for both the effectiveness and safety analyses.

In addition, 15 subjects were enrolled as part of the initial, non-randomized phase of the study. These are subjects who were not randomized and will not be included in the primary endpoint analysis. They did, however, undergo all follow-up visits and their data have been reported separately (IDE S003, 03May2019, Attachment T). Thus, a total of 192 subjects were enrolled in the IDE study. Details about the justification of sample size for primary effectiveness and safety endpoint can be found in Sections 5.1 and 5.2.

Subject recruitment will take place at up to 25 active investigational sites in the United States, with no more than 20% of the total randomized population (40 subject maximum) enrolled at any single site.

## 5.1 Justification of Sample Size for Primary Effectiveness Endpoint

Sample size requirements were based on the assumption that the composite endpoint rates for the proposed clinical trial will be similar to those reported in the literature from 2006-2013. It was assumed that at 6 months, 82% of subjects in the MicroStent® arm will demonstrate primary patency while 60% of PTA arm subjects will demonstrate primary patency. As displayed below, a total of 177 subjects (117 MicroStent® System and 60 PTA) is required to achieve 80% power to detect the difference using a 1-sided Fisher Exact test with alpha of 0.025. The table displays the power for MicroStent failure rates to range between 12% and 18% as well as corresponding differences which allow one-sided p=0.025 superiority to be achieved.

**Two group Fisher Exact test: Null is equal proportions (odds ratio = 1) (unequal n's)**

| | 80% Power | | | Reach 2-sided p=0.05 | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** |
| **Test significance level, a** | 0.025 | 0.025 | 0.025 | 0.025 | 0.025 | 0.025 |
| **1 or 2 sided test?** | 1 | 1 | 1 | 1 | 1 | 1 |
| **MicroStent failure rate, $p_1$** | 0.120 | 0.150 | 0.180 | 0.120 | 0.150 | 0.180 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Control failure rate, $p_2$** | 0.320 | 0.360 | 0.400 | 0.249 | 0.288 | 0.326 |
| **Power (%)** | 84 | 83 | 83 | 50 | 50 | 50 |
| **$n_1$** | 117 | 117 | 117 | 117 | 117 | 117 |
| **$n_2$** | 60 | 60 | 60 | 60 | 60 | 60 |

## 5.2 Justification of Sample Size for Primary Safety Endpoint

Rocha-Singh et al. (1) reported that 8.4% (9/107) of subjects treated for CLI with a self-expanding stent had major amputations within 6 months following treatment (n=8) or died within 30 days (POD) (n=1).

In a meta-analysis of patients treated for CLI using PTA, Mustapha et al. (2) estimated a 1-year amputation rate of 14.9% based on the results of 37 studies. Assuming the 6-month rate to be half the 1-year rate suggests a 7.45% amputation rate at 6 months. The meta-analysis did not include POD as an endpoint. Thus, it appears appropriate to assume that the 6-month major amputation + POD rate for both the MicroStent® arm and PTA arm is approximately 8%. Given that both of the referenced studies included Rutherford 6 subjects and a minimal number of Rutherford 3, it is reasonable to assume that the rates of MALE + POD events in this study (Rutherford 4-5) will be lower because enrolled subjects will be healthier than those reported in the literature. Thus, sample size requirements were based on the assumption that the MALE + POD rates are approximately 5% for both treatment groups. For a noninferiority margin of 10%, a total of 177 subjects (117 MicroStent® System and 60 PTA) is required to achieve 80% power with alpha of 0.025 using a one-sided exact test for the difference between two proportions. The table displays the power for MALE + POD rates to range between 2% and 5% as well as corresponding differences which allow one-sided p=0.025 non-inferiority to be achieved.

**Upper confidence limit for difference in proportions (simulation) (unequal n's)**

| | 80% Power | | | | Reach Non-inferiority | | | |
|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| **Confidence level, 1-a (1-sided)** | 0.975 | 0.975 | 0.975 | 0.975 | 0.975 | 0.975 | 0.975 | 0.975 |
| **Control failure rate, $p_S$** | 0.050 | 0.040 | 0.030 | 0.020 | 0.050 | 0.040 | 0.030 | 0.020 |
| **MicroStent failure rate, $p_T$** | 0.050 | 0.040 | 0.030 | 0.020 | 0.077 | 0.065 | 0.050 | 0.040 |
| **Upper limit for $p_T$ - $p_S$, UL** | 0.100 | 0.090 | 0.080 | 0.075 | 0.100 | 0.090 | 0.080 | 0.075 |
| **Number of simulations** | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |
| **Random seed for simulations** | 123 | 123 | 123 | 123 | 123 | 123 | 123 | 123 |
| **Power (%)** | 85 | 84 | 81 | 88 | 50 | 50 | 50 | 50 |
| **$n_S$** | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| **$n_T$** | 117 | 117 | 117 | 117 | 117 | 117 | 117 | 117 |

# 6 Statistical Analyses

## 6.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) or

other widely-accepted statistical or graphical software as required.

The significance of differences between independent groups, such as treatment arm, involving continuous data will be tested using an unpaired t-test. Analysis of categorical data will utilize the Fisher Exact test to evaluate the significance of differences. Analysis of ordinal data will utilize Wilcoxon Rank Sum test to evaluate the significance of differences between groups. Superiority testing will be 2-sided where two-sided p-values < 0.05 will indicate statistically significant differences. A non-inferiority test (primary safety) will be one-sided where one-sided p-values <0.025 will indicate non-inferiority relative to a pre-specified offset. Time to event analyses (i.e. Kaplan-Meier) will be conducted as a sensitivity analysis for all proportion-based assessments where follow-up may be censored; an unstratified log rank test will be used to compare treatment groups. For the primary safety and effectiveness endpoints, the 6-month analysis will be considered primary. Supportive analyses of these outcomes through 12 months will also be provided.

[redacted]

The study will be considered successful if the primary effectiveness and safety endpoints are both met.

### 6.1.1 Descriptive Statistics

Data that are of a continuous nature, such as age and vessel diameter, will be summarized by the mean, median, 1st quartile, 3rd quartile, standard deviation, minimum and maximum. The number of observations upon which these statistics are computed will also be presented. Data that are categorical, such as gender and race, will be summarized as frequencies and percentages and include n/N where n is the number of observations in the category and N is the total number of observations across all categories. Percentages will be displayed with up to 1 decimal place with the exception of percentages <0.05 which may be displayed with up to 4 decimal places.

### 6.1.2 Study Day

Day in study will be calculated relative to the index procedure as follows:

Study Day = Assessment Date – Index Procedure Date + 1

For each subject, duration in study will be based on last study contact date which is the latest date between follow-up visits, assessments, adverse event onset or resolution, and study exit including date of death.

### 6.1.3 Visit Windows

Analysis windows for effectiveness will be defined as follows: 1 month (days 1-37), 3 months (days 38-104), 6 months (days 105-210), 1 year (days 211-420), 2 years (days 421-790), and 3 years (days 791-1155). Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless if it is out of window. For data analyzed based on the nominal visit as entered in the CRF, if the visit occurred between visits, then the data will be included for analysis independent of nominal visit timing, For analysis involving duplex or angiographic image results at a specific visit, the Core Lab will report findings at that time point.

Given the interest in effectiveness outcomes over the first year, tables will be presented for 6 month (primary) and 12 month (supportive) milestone outcomes in accordance with the pre-specified study windows.

For safety events, subjects with events occurring at any time will be counted as having events while subjects without events will be considered event-free. For Kaplan-Meier analysis, point estimates corresponding to nominal visit time points (e.g. 6 month, 12 month, etc.) will be based on the actual event day unless otherwise noted.

### 6.1.4 Statistical Significance

P-values will be rounded to four decimal places. If a p-value is less than 0.0001, it will be reported as “<0.0001”. If a p-value is greater than 0.9999, it will be reported as “>0.9999”. Survival analyses (i.e. Kaplan-Meier) may be conducted as a sensitivity analysis for all proportion based assessments where follow-up may be censored.

### 6.1.5 Protocol Deviations

Protocol deviations will be reported by the investigational sites in the electronic database. Protocol deviations will be categorized as major and minor. Protocol deviations will be classified as follows:

Major

- Inclusion/exclusion criteria
- Study interventional procedures not performed as specified in the protocol or device labeling.

Minor

- Assessment not done or done outside of window
- Assessment out of window
- Follow up procedures not done as specified in protocol
- Events not reported per protocol
- AE not reported per protocol
- COVID - Assessment not done or done outside of window
- Informed Consent
- Inadequate consent
- Protocol-required visit not completed
- Protocol-required assessment not completed
- Protocol-required visit completed outside of follow-up window
- Expired stent.

The deviations will be reviewed as to whether they affect the scientific integrity of the study in defining the per protocol population.

Protocol deviations will be presented for each category and for each treatment group separately. Incidence rates will be compared using a two-sided Fisher Exact test.

In addition, complete listings of protocol deviations will be provided.

[redacted]

The methodologies in this SAP address the randomized phase of this study only.

## 6.2 Analysis Populations

The following populations are presented for analysis:

1. **Modified Intent-to-treat (mITT):** Subjects will be grouped for comparison according to the treatment to which they were randomized, regardless of the actual treatment received and follow-up duration. Analysis using the mITT population will be performed using a modified intent-to-treat principle; i.e., any screen failed subjects that were randomized (delayed screen failure) but not treated will be noted in the CONSORT chart as randomized but will be excluded from any analyses. Populations for the two primary effectiveness analyses (FDA-defined vs. Sponsor-defined) will differ based on the availability of documented occlusions.
2. **As treated (AT)**: Subjects will be grouped for comparison according to the treatment they actually received for safety analyses.
3. **Per protocol (PP)**: Subjects who complete the study without major protocol violations. The reasons for not being included in the PP population will be reported. The definition of a major protocol violation, and thus which subjects will be excluded from the PP population, will be finalized prior to analysis of the primary endpoints.

Reflecting data availability within pre-defined windows, the primary effectiveness endpoint will be tested using the modified intent-to-treat (mITT) population of study subjects as described above. Effectiveness analyses will be repeated using the per protocol (PP) population if the PP population excludes >5% of the mITT population. The primary analysis for all other evaluations will similarly use the modified intent-to-treat principle for analysis as described above. The safety population will be based on the AT population.

## 6.3 Missing Data Strategy

Primary and secondary effectiveness endpoint data will be analyzed utilizing the mITT population. This analysis population will also be used for the sensitivity analysis addressing the robustness of study results. Although every effort will be made to ensure subjects return for each follow-up visit and all required tests are completed, there will be instances when visits are missed, or test results are not available. These situations will be reviewed for impact in a consistent manner prior to database lock at a Biostatistics Data Review Meeting (BDRM).

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

## 6.4 Subject Disposition

The number of subjects in each analysis population will be presented along with reason for any exclusions. The accounting will provide the reason for exclusion from the primary effectiveness endpoints. Subject accountability will be summarized by visit. The number of subjects who are randomized, eligible for follow-up, and number completing clinical and required duplex imaging follow-up will be summarized for each protocol-required visit. In addition, the number of subjects who complete the study will be provided in addition to timing and reasons for early exit. In addition, any



[redacted]

withdrawals representing intercurrent events will be provided. Differences between treatment groups for the time-to-end of study will be assessed using an unstratified log rank test.

## 6.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for clinically-relevant demographics, baseline clinical characteristics, medical and surgical history, and baseline lesion characteristics. Fisher Exact tests will be used to compare treatment groups for categorical data; Wilcoxon Rank Sum tests will be used to compare treatment groups for ordinal data, while unpaired t-tests will be used to compare continuous data.

## 6.6 Device Failures and Malfunctions

Device performance was to be evaluated by the treating physician.

*Device Failure:* A device has failed if it does not perform according to labeling and negatively impacts the treatment while used according to the labeling.

*Device Malfunction*: A device malfunction is an unexpected change to the device that is contradictory to the labeling and may or may not affect device performance.

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 CRF.

If there are any device failures or malfunctions, then a listing will be presented separately for MicroStent.

## 6.7 Procedural Success

MicroStent and PTA represent different approaches for achieving target lesion patency.

Procedural success will be assessed separately for each approach with a common start prior to subject randomization. For both treatment arms, the guidewire must cross the target lesion (TL) before randomization to treatment arm and device delivery to TL. The treating physician and angiographic Core Lab will evaluate procedural success components as displayed below.

| Treating Physician Assessed Metrics | MicroStent | PTA |
|---|---|---|
| Device Positioned in TL to fully extend over occlusion | X | X |
| Pre-dilation of TL | X | N/A |
| Visualization of Stent During Deployment | X | N/A |
| Post dilation of Stent | X | N/A |
| Residual Stenosis post treatment (% diameter stenosis) | X | X |
| Any device-related issues | X | X |
| Bailout procedures to obtain satisfactory results (Y/N) | X | X |
| Bailout Reason | X | X |
| Bailout Treatment Type | X | X |

| Core Lab Assessed Metrics | MicroStent | PTA |
|---|---|---|



[redacted]

| | | |
|---|---|---|
| Post Treatment Vessel Integrity (staining, perforation, dissection, distal embolization) | X | X |
| Stent Migration | X | N/A |
| Stent Integrity (fracture, apposition) | X | N/A |
| Diameter Residual Stenosis post treatment | X | X |

Procedural Success is expected for all but a few subjects (<5%). Listings will be generated for any subjects with any metric failures. In addition, narratives will be prepared for any subject declared as a Procedural Failure (including bailouts and any stent subjects crossed over to PTA). Each narrative will indicate the individual metrics where failure was recorded.

## 6.8 Analysis of Study Endpoints

### 6.8.1 Primary Safety Endpoint

*Primary Safety Endpoint*: A composite of freedom from perioperative death (POD) at 30-days and freedom from MALE at 6 months post index procedure.

The definition of MALE includes above the ankle amputation of the index (or target) limb and/or major reintervention with involvement of the target lesion (new bypass graft, jump/interposition graft revision, thrombectomy, and/or thrombolysis). Study subjects will be assigned to one of two categories: 1) Those who experience a primary safety event (die within 30 days of their index procedure or experience one or more MALE within 6 months (up to Day 210) and 2) those who do not experience a primary safety event. It is expected that the proportion of subjects in the MicroStent® arm who do not experience a primary safety event will not be inferior to the proportion of subjects in the PTA arm who do not experience such events.

#### 6.8.1.1 Primary Safety Endpoint Analysis

In statistical terms the null ($H_0$) and alternative ($H_A$) hypotheses are:

$$H_0: p_{MS} \leq p_{PTA} - \delta$$

$$H_A: p_{MS} > p_{PTA} - \delta$$

where $p_{MS}$ is the proportion of subjects in the MicroStent® arm who do not experience a primary safety event, $p_{PTA}$ is the proportion of subjects in the PTA arm who do not experience a primary safety event and $\delta$ is a noninferiority margin of 0.1 (10%).

The endpoint will be analyzed using the AT population. The numerator for the proportion in each arm will include subjects free from a primary safety event within 210 days and the denominator will include subjects with a primary safety event within 210 days in addition to subjects considered free from event. The hypothesis will be tested using a one-sided Farrington-Manning test for the difference between two proportions. If the p-value associated with the test statistic is < 0.025, the null hypothesis will be rejected in favor of the alternative hypothesis and the safety of the MicroStent® System will be demonstrated.

### 6.8.1.2 Additional Primary Safety Analysis

Additional pre-planned primary safety endpoint analyses will be conducted as follows;

- Analyses considering only device-related events. The endpoint will be analyzed as described for the primary analysis in Sections 6.8.1.1 and 6.8.3.1, with the exception that the numerator of the proportion will include subjects that are free from a *device related* event. Device relatedness is determined by the investigator and adjudicated by the Clinical Events Committee (CEC). CEC adjudication data will be used for the analysis.
- The endpoint will be analyzed using Kaplan-Meier analysis methods through 6 months. Differences between groups will be assessed using an unstratified log-rank test. Time to event will be based on the earliest event occurrence or last contact date for subjects who are censored. Subjects with time to event or censoring greater than 210 days will be censored at 210 days in the analysis.
- The primary safety endpoint and the above two additional analyses will be extended to 12 months post index procedure. The As Treated principle will be extended to 12 months (up to Day 420). This includes (1) subjects with any POD or MALE within 12 months (up to Day 420) and (2) those who do not experience a primary safety event. CEC adjudication data will be used for the analysis inclusive of device relationship.

## 6.8.2 Primary Effectiveness Endpoint

*Primary Effectiveness Endpoint*: The Sponsor-defined primary patency isdefined as freedom from: a) bail-out procedure, b) target lesion occlusion treated with clinically driven target lesion reintervention (CD-TLR) through 6 months of follow-up (up to Day 210), and ) target limb major amputation through 6 months of follow-up (up to Day 210). It is hypothesized that the proportion of subjects with primary patency at 6 months will be higher among subjects in the MicroStent® arm than subjects in the PTA arm.

In statistical terms, the null ($H_0$) and alternative ($H_A$) hypotheses are:

$$H_0: p_{MS} \leq p_{PTA}$$

$$H_A: p_{MS} > p_{PTA}$$

where $p_{MS}$ is the proportion of subjects in the MicroStent® arm demonstrating primary effectiveness at 6 months and $p_{PTA}$ is the proportion of subjects in the PTA arm demonstrating primary effectiveness at 6 months (up to Day 210) according to the Sponsor definition.

The proportion of subjects in the MicroStent® arm who demonstrate primary effectiveness at 6 months will be compared to the proportion of subjects in the PTA arm who demonstrate primary effectiveness at 6 months using a Fisher Exact test. If the 1-sided p-value associated with this test is < 0.025 and the proportion of subjects with primary patency in the MicroStent® arm is higher than the proportion for

subjects in the PTA arm, the null hypothesis will be rejected in favor of the alternative hypothesis and the effectiveness of the MicroStent® in achieving primary patency will be demonstrated.

[redacted]

### 6.8.2.1 Primary Effectiveness Missing Data Handling

See Section 6.3 for details regarding primary effectiveness missing data handling.

### 6.8.2.2 Supportive Primary Effectiveness Analyses

Additional pre-planned analyses of the primary effectiveness endpoint will be conducted as follows to further assess device relationship:

- Analyses considering freedom from both: a) device-related target lesion occlusion treated with

device-related CD-TLR and b) device-related target limb major amputation through 6 months of follow-up. Three definitions follow:

A device-related event, typically an undesirable effect, is an event caused or connected to the medical device relative to its performance, safety or usability; assignment of relatedness, causality or connection is made by the device-user and/or CEC adjudication.

A device-related occlusion, such as an occlusion of the treated/target lesion zone, is reported by the device-user or clinical research site to be device-related and to be confirmed by Core Lab evaluation and/or adjudicated interventions.

A device-related CD-TLR, such as a clinically-driven target lesion reintervention that has a direct causal relationship to the medical device, where causality assignment or relationship is made by the device-user or external CEC adjudication as possible device-related events.

These analyses will not be presented if there are no device-related events per device-related category.

- An analysis considering freedom from both: a) target lesion occlusion treated with TLR and b) target limb major amputation through 6 months of follow-up
- Primary effectiveness endpoint results (proportions-based analysis) will also be presented through 12 months (up to Day 420) as a supportive analysis. Subjects with a bail-out procedure, target lesion occlusion treated with CD-TLR through the 12 month milestone (up to 420 days), or major amputation through the 12 month milestone (up to 420 days) will be counted as primary patency failures.
- The endpoint will be analyzed using Kaplan-Meier analysis methods through 12 months. The Kaplan-Meier estimate of primary patency at 6 and 12 months will be based on the point estimate at 180 and 360 days respectively. Kaplan-Meier analysis will also be presented to the end of the follow-up window (420 days) to account for the protocol allowed visit window. Time to event will be based on the earliest event occurrence or last contact date for subjects who are censored. Note that for subjects with failure due to bailout procedure, timing of failure will be considered at 1 day for this analysis. For analysis presented through 360 days, subjects with follow-up greater than 360 days will be censored at 360+1 days. For analysis presented through 420 days, subjects with follow-up greater than 420 days will be censored at 420 + 1 days in the analysis. Differences between groups will be assessed using the log-rank test.
- Time to target lesion occlusion will also be analyzed. A Kaplan-Meier lifetable will be constructed for the time to the first occlusion which will ignore all re-interventions. The first occlusion will be determined solely from the diagnostic and non-diagnostic Core Lab forms indicating target lesion occlusion where the earliest occurrence defines the first occlusion event and the time to the first occlusion event. The time to the first occlusion would be flagged 1 at the first Occlusion Yes event; otherwise, if no Occlusion Yes events, censoring occurs at the last follow-up time when there was a No occlusion evaluation and the occlusion flag is set equal to 0 if Occlusion No. Otherwise, subjects with

no occlusion data are excluded from this analysis.

- Per-protocol analysis will be performed for the primary effectiveness endpoints if the Per-protocol population excluded >5% of the As Treated population.

### 6.8.3 Secondary Endpoints

#### 6.8.3.1 Secondary Safety Endpoints

*Secondary Safety Endpoint #1*: Freedom from major adverse limb events (MALE) at all timepoints. The number and percentage of subjects who did not experience MALE will be presented for both treatment arms separately. This analysis uses the AT population.

*Secondary Safety Endpoint # 2*: Frequency and severity of serious adverse events and device and procedure-related adverse events at any time during the study if qualified to be confirmed by the CEC. The secondary safety endpoint utilizes data collected on adverse events that occur throughout the course of the study subject to CEC adjudication. The intent is to construct a safety profile for the MicroStent® Device and procedure relatedness will rely upon the investigator reported outcomes unless CEC adjudicated. This analysis uses the AT population.

Device related adverse events are only to be associated with the MicroStent and not the PTA device, as the device under investigation is the MicroStent. The frequency and severity of serious adverse events and adverse events judged to be device and/or procedure-related will be summarized for subjects treated with the MicroStent® separately from those that occur among subjects treated with PTA only. Similar events will be categorized and the frequency of events, number of subjects who experience them along with severity will be tabulated. In addition, detailed patient lists of each serious adverse events and device and/or procedure-related adverse event will be provided and include a description of the event, severity, duration, treatment for the event and outcome.

#### 6.8.3.2 Secondary Effectiveness Endpoints

There are two secondary effectiveness endpoints with hypotheses to be tested. The first is freedom from target limb major amputation (above the ankle) at 6 months (up to Day 210) post index intervention. The second is reduction in size of leg/foot ulcers at 6 months post index intervention. Hypothesis testing of these secondary endpoints will be conducted only after both primary endpoints have been met in order to preserve the overall Type I error rate.

Hierarchical testing will be used to control the family-wise error rate in the order specified below. Testing will continue as long as two-sided $p<0.05$ (or one-sided $p<0.025$) in favor of the MicroStent® vs. PTA.

*Secondary Effectiveness Endpoint #1*: Freedom from major amputation (above the ankle) at 6 months post index intervention.

It is hypothesized that the proportion of subjects without major amputation at 6 months will be higher among subjects in the MicroStent® arm than subjects in the PTA arm. In statistical terms the null ($H_0$) and alternative ($H_A$) hypotheses are:

$H_0$: $p_{MS} \leq p_{PTA}$

$H_A$: $p_{MS} > p_{PTA}$

where $p_{MS}$ is the proportion of subjects in the MicroStent® arm without major amputation at 6 months and $p_{PTA}$ is the proportion of subjects in the PTA arm without major amputation at 6 months. Only major amputations of the target limb will be considered failures of the endpoint.

The proportion of subjects in the MicroStent® arm who have not undergone major amputation by 6 months (up to Day 210) will be compared to the proportion of subjects in the PTA arm who have not undergone major amputation at 6 months using a Fisher Exact test. If the 1-sided p-value of this test is less than or equal to the critical value and the proportion of subjects in the MicroStent® arm without major amputation is higher than the proportion for subjects in the PTA arm, the null hypothesis will be rejected in favor of the alternative hypothesis and the effectiveness of the MicroStent® System in preventing major amputations will be demonstrated. Proportions and their 2-sided 95% exact binomial confidence intervals will also be reported. Additionally, the difference between arms with corresponding two-sided 95% exact confidence interval and the 2-sided Fisher Exact test p-value will be presented.

In addition, time until major amputation will be analyzed using the Kaplan-Meier method. Time will be computed as the number of days between index treatment and 1) last study contact including date of withdrawal or last follow-up visit including death or 2) date of major amputation whichever occurs first. Major amputation will be regarded as a terminal event. Cumulative survival rates through 6 months will be displayed graphically for each treatment arm separately. The significance of differences between the two treatment arms will be tested using the log rank test.

These analyses will be repeated for outcomes at 12 months (up to Day 420) but not as part of the hierarchical testing plan.

*Secondary Effectiveness Endpoint #2*: Reduction in size of leg/foot ulcers at 6 months post index intervention.

The area of leg/foot ulcers distal to arterial lesions will be measured using specialized wound cameras during physical examination prior to treatment (baseline visit) and at each follow-up visit. These cameras measure and calculate the area of wounds automatically. Wound size change scores will be computed by subtracting measurements at baseline from those obtained at follow-up such that negative scores indicate a reduction in wound size and positive scores indicate an increase. It is expected that, on average, subjects in the MicroStent® arm will demonstrate greater reduction in wound size at 6 months than subjects in the PTA arm. In statistical terms, the null ($H_0$) and alternative ($H_A$) hypotheses are:

$H_0$: $\mu_{PTA} \geq \mu_{MS}$

$H_A$: $\mu_{PTA} < \mu_{MS}$

where $\mu_{MS}$ is the mean wound size change score (baseline – follow-up) of subjects in the MicroStent® arm at 6 months and $\mu_{PTA}$ is the mean change score of subjects in the PTA arm at 6 months.

Change score summary statistics including the mean, standard deviation, median and interquartile range will be computed and presented for each treatment arm separately. Wound size change scores among subjects in the MicroStent® arm will be compared to change scores among subjects in the PTA arm using a Wilcoxon rank sum test. If the 1-sided p-value of this test is less than the critical value and the mean change score for the MicroStent® arm is less than the mean change score for subjects in the PTA arm, the null hypothesis will be rejected in favor of the alternative hypothesis and the effectiveness of the MicroStent® System in reducing leg/foot ulcers will be demonstrated.

This analysis will include only subjects presenting with leg/foot ulcers prior to their index treatment (baseline) and who complete their 6-month visit. If a wound assessment corresponding to the 6 month visit is not available but the last available post-baseline assessment prior to 6 months shows the wound has healed, the last available wound assessment will be used in the analysis.

These analyses will be repeated for outcomes at 12 months (up to Day 420), but not as part of the hierarchical testing plan.

### 6.8.3.3 Exploratory Effectiveness Endpoints

[redacted]

[redacted]

## 6.9 Poolability Analyses

Data will be analyzed to evaluate whether data from the various study sites can be pooled. Results will be reported by site and/or pre-defined geographic regions as per the previous FDA clinical study report submission.

[redacted]

Heterogeneity among study sites in the estimated treatment effect on each outcome will be tested using the interaction between randomized arm and site in a logistic regression with the respective primary endpoint as a binary outcome. If the 2-sided p-value associated with the interaction test is < 0.15, the variable will be deemed to vary significantly between study sites.

## 6.10 Safety Analyses

Adverse events (AE) will be reported for the AT population. AEs will be tabulated with the number of events and subjects with event for each event type and overall. Rates will be reported as the number of subjects who experience at least one event during the analysis interval out of the total number of subjects with follow-up to the beginning of the analysis interval (e.g. for summary of AEs through 12 months (up to Day 420), the denominator will include all randomized subjects as treated). Serious adverse events, major adverse limb events (MALE), procedure-related adverse event, device-related adverse event, serious adverse device effect (SADE), and unanticipated adverse device effect (UADE) will also be tabulated using site-reported data reflecting CEC adjudicated data (if CEC adjudication is available for an event, then that will be used in summary tables; otherwise, site-reported data will be used).

A listing of all subject deaths with corresponding adverse event information will be reported.

All device deficiencies will be reported in listing format. Any stent migration or stent fracture reported by the angiographic core lab will be reported.

## 6.11 Subgroup Analyses

Assessment of the effects of a number of baseline and treatment variables on the primary safety and effectiveness endpoints will be conducted. These variables include:

- Age (≤ 75 / > 75)
- Gender (Male / Female)
- Race (Caucasian, African American, Hispanic, Asian, Other) - At the time of analysis, in the event that numbers of small or non-existent, categories may be collapsed to Caucasian vs. Other.
- BMI (Normal/Overweight/Obese)

- Current smoking status (Current/Former/Never)
- Diabetes (Yes/No)
- Hypertension (Yes/No)
- Chronic kidney disease (Yes/No)
- Rutherford classification at the time of enrollment (4, 5-6)
- Most distal target lesion location (Proximal/Middle/Distal)
- Severity of calcification (None or Mild/Moderate/Severe)
- Lesion length (<4.0 cm/4.0-5.9 cm/≥6.0 cm)
- Target lesion total occlusion at baseline.

The effect of each subgroup will be evaluated with a Fisher Exact test to assess overall subgroup effects and using a K 2x2 test to assess odds ratio homogeneity. These analyses are intended to demonstrate consistency of the treatment effect across subgroups. Within each subgroup, the endpoint will be presented as a proportion within each arm well as the odds ratio for treatment vs. control with corresponding two-sided 95% confidence interval.

## 6.12 Other Analyses

### 6.12.1 Treatment Procedure Data

Treatment data will be collected and reported by the study site for both the MicroStent® arm and PTA arm. The number of times each device size is used, number of procedures per subject, number of times difficulties with either the device or procedure are encountered, and any procedure-related or device-related adverse events will be summarized separately in tables and listings for the qualifying CEC adjudicated events as well as for the site-reported events not requiring adjudication. A listing will be created for any procedures performed subsequent to the index procedure including reason for the procedure, type of procedure (PTA, Stent, bypass, etc.) and whether it is performed on a lesion treated at the index procedure during the study.

### 6.12.2 Concomitant Medications

Anti-platelet and anti-coagulant usage will be summarized in tables and listings reporting the number of subjects on these medications at each timepoint. Additionally, a summary of subjects receiving a dual antiplatelet therapy (DAPT) regimen will be compiled for each time point.

# 7 Changes from Planned Analyses

[redacted]

[redacted]

# 8 Subject Listings

Listings will be provided for the clinical study report (CSR) which will include the following data source specific information. The data listed below will be included in separate listings or combined as applicable to provide the relevant information from the sites and the CEC adjudication for the CSR. Representative listings include the following to meet subject-level reporting requirements.

1. Subject disposition;
2. Listing of subjects excluded from the AT and PP analysis populations with reason;
3. Clinically relevant demographic and baseline characteristics;
4. Medically relevant characteristics for subjects with minor amputations and occlusions;
5. Subjects with POD or MALE including whether the event was device related;



[redacted]

6. Primary patency status at 6 and 12 months;
7. All serious adverse events with timing and category (MedDRA SOC, PT) according to CEC adjudication;
8. Subjects with target lesion occlusion including timing
9. All Adverse Events;
10. All Subjects Deaths;
11. All Protocol Deviations;
12. All Device Deficiencies;
13. Subjects prematurely exiting the study with reasons specified.

# 9 References

1. Rocha-Singh KJ, et al. Major Adverse Limb Events and Wound Healing Following Infrapopliteal Artery Stent Implantation in Patients with Critical Limb Ischemia. *2012, Cath and Cardiovasc Interv, Vol. 80, pp. 1042-51.*
2. Mustapha JA, et al. Percutaneous Transluminal Angioplasty in Patients with Infrapopliteal Arterial Disease. 2016, Circ Cardiovasc Interv.
3. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg, 58(1S), S1-S109 e133 (2019).
4. Stoner MC, Calligaro KD, Chaer RA, Dietzek AM, Farber A, Guzman RJ et al. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. J Vasc Surg, 64(1), e1-e21 (2016).

# 10 Appendices

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# SAP ADDENDUM

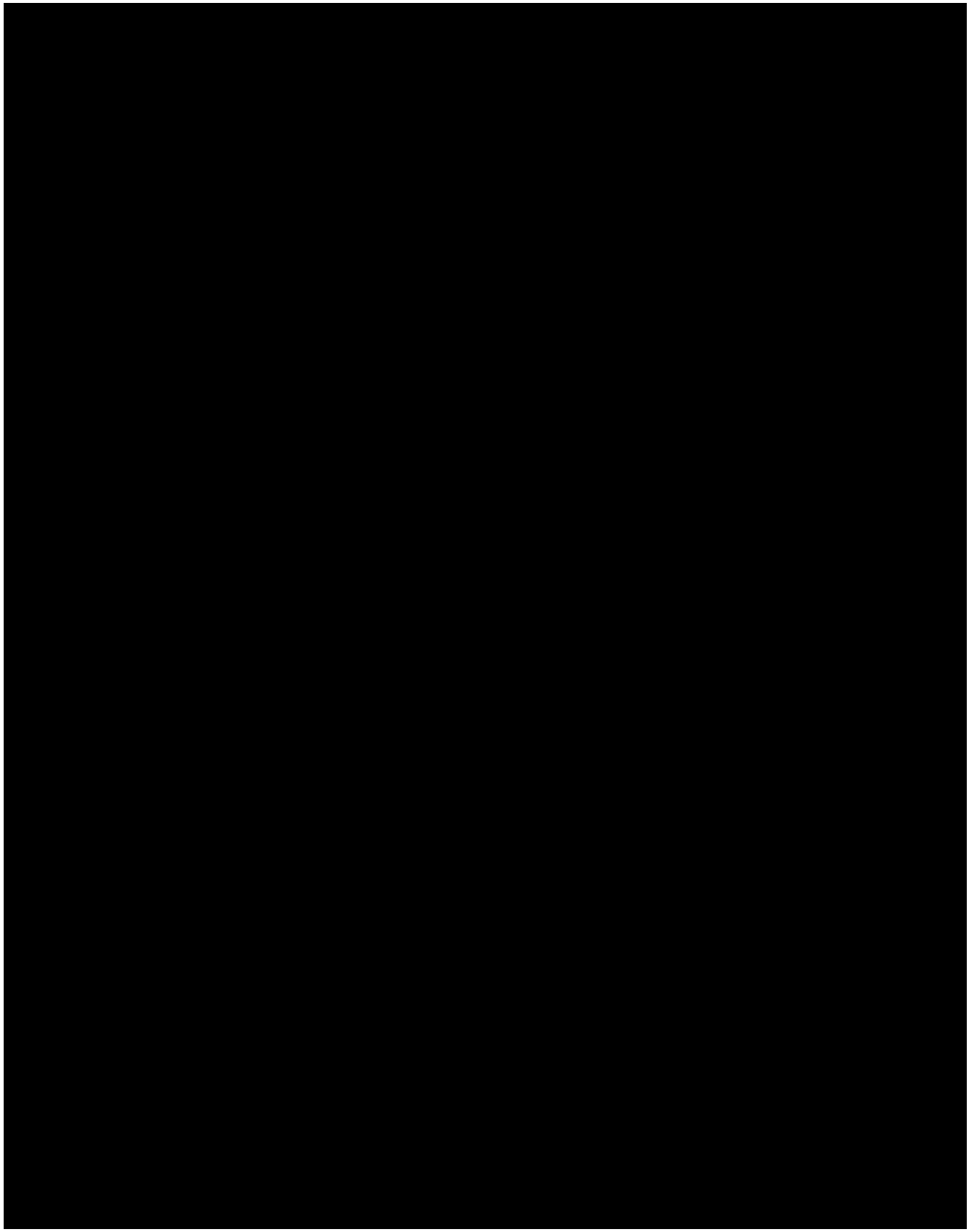
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