Reflow Medical Wingman Catheter Wing-IT Clinical Trial
RFM-CTO-13001
NCT03403426
Document Date: 20-MAY-2019

Statistical Analysis Plan

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ABBREVIATIONS AND ACRONYMS

Acronym	Description
ABI	Ankle-Brachial Index
AE	Adverse Event
BMI	Body Mass Index
CEC	Clinical Events Committee
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
IFU	Instructions for Use
IRB	Investigational Review Board
ITT	Intention-to-Treat
LCL	Lower Confidence Limit
MAE	Major Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
PAD	Peripheral Arterial Disease
PP	Per Protocol
PTA	Percutaneous Transluminal Angioplasty
PRO	Patient-reported Outcomes
QVA	Quantitative Vascular Angiography
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SD	Standard Deviation
SFA	Superficial Femoral Artery

TLF	Tables, Listings and Figures
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
UADE	Unanticipated Adverse Device Effect

Statistical Analysis Plan

1 INTRODUCTION

The purpose of this clinical study is to evaluate the safety and effectiveness of the Wingman Catheter used to cross chronic total occlusions in infrainguinal peripheral arteries that failed crossing attempts with conventional guidewires. The Wingman Catheter is a percutaneous device that is designed to cross occlusions by using an extendable guide tip to dotter and penetrate through the plaque to create a channel. The Wingman Catheter is intended to be used in conjunction with standard endovascular devices and fluoroscopic guidance.

1.1 Design, Treatments and Visits

This is a prospective, multi-center, non-randomized single arm study of the Wingman Catheter to cross a single infrainguinal peripheral chronic total occlusion. This study will be conducted at up to twelve (12) investigational sites in North America and three (3) centers in Europe. Safety and efficacy will be evaluated during the index procedure through 30-day follow-up. The primary endpoint of this study is to assess crossing success with the Wingman device identified as confirmation of guidewire placement in the distal true lumen. The primary safety endpoint of this study will evaluate in-hospital and 30-day MAEs and clinically significant perforations. Secondary endpoints include the lesion (<50% final residual stenosis and grade 'C' or greater dissections created during the procedure that is not resolved by visual estimate) procedural success and safety rates; and the evaluation of procedural and fluoroscopic time/contrast volume. Patient follow-up will be recorded through 30 days post procedure.

1.2 Objectives

The Wingman device received FDA 510(k) clearance in August 2011 and February 2012 for use as a guidewire support device. Since then the device has been used in approximately two thousand five hundred (2500) commercial cases across centers within the US and globally to access discrete regions in the peripheral vasculature. This clinical study has been designed to assess the ability of the Wingman Catheter to facilitate crossing of CTOs in infrainguinal peripheral arteries. The Wingman's ability to access and facilitate crossing of CTOs is an important first step towards gaining access to treat these difficult lesions and securing guidewire positioning for therapeutic treatment.

1.3 Subject Population

Subjects with symptomatic peripheral arterial disease (PAD) requiring revascularization. A maximum of 85 subjects > 18 years of age, meeting all the following inclusion and none of the exclusion criteria, and who are willing to sign informed consent will be enrolled.

Patients must meet <u>all</u> the following inclusion criteria to be eligible for enrollment in this trial:

1) Patient is willing and able to provide informed consent.
2) Patient is willing and able to comply with the study protocol.
3) Patient is > 18 years old.
4) Patient has peripheral arterial disease requiring revascularization as evidenced by contrast, CT or MR angiography.

5) A maximum of 2 lesions can be treated per patient, as identified by the investigator, that have occluded infrainguinal arteries that are 99-100% stenosed and no flow is observed in the distal lesion except the flow from collateral circulation.
6) Target lesion is ≥ 1 cm and ≤ 30 cm in length by visual estimate.
7) Target vessel is ≥ 2.0 mm in diameter.
8) Patient has Rutherford Classification of 2-5.
9) Lesion cannot be crossed by concurrent conventional guidewire.
10) Reconstitution of vessel at least 2cm above bifurcation/trifurcation.
11) Occlusion can be within previously implanted stent.

Patients will be excluded from this trial if any of the following criteria are met:

1) Patient has a known sensitivity or allergy to contrast materials that cannot be adequately pre-treated.
2) Patient has a known sensitivity or allergy to all anti-platelet medications.
3) Patient is pregnant or lactating.
4) Patient has a co-existing disease or medical condition contraindicating percutaneous intervention.
5) Target lesion is in a bypass graft.
6) Patient has had a failed crossing attempt without an intervening intervention on the target limb within the past 14 days.
7) Patient has a planned surgical or interventional procedure within 30 days after the study procedure.

1.4 Sample Size Considerations

The exact binomial distribution is used for calculation of the sample size. The hypotheses and sample size calculations provided in the clinical study protocol are as follows.

The null and alternative hypotheses of the primary efficacy endpoint are:

H_0: $\pi_{Wingman\_efficacy} \leq \pi_{PG\_efficacy} - \delta_{efficacy}$

H_A: $\pi_{Wingman\_efficacy} > \pi_{PG\_efficacy} - \delta_{efficacy}$

where,

$\pi_{PG\_efficacy}$ = PG success rate

$\pi_{Wingman\_efficacy}$ = Wingman device success rate

Literature Review[1-11] indicates that the average success rate of several CTO catheter device types is 83.2%. Using this rate as the historical control and using a non-inferiority margin ($\delta_{efficacy}$) of 12.5% the hypotheses of the primary efficacy endpoint can be rewritten as:

H_0: $\pi_{Wingman\_efficacy} \leq 70.7\%$

H_A: $\pi_{Wingman\_efficacy} > 70.7\%$

The null and alternative hypotheses of the safety endpoint are:

H_0: $\pi_{Wingman\_safety} \geq \pi_{PG\_safety} + \delta_{safety}$

H_A: $\pi_{Wingman\_safety} < \pi_{PG\_safety} + \delta_{safety}$

where,

π_{PG_safety} = PG major adverse event rate

$\pi_{Wingman\_safety}$ = Wingman device major adverse event rate

Literature Review[1-11] indicates that the average rate of major adverse events, perforations, grade C or higher dissections and embolizations is 5.0%. Using this rate as the historical control, and using a delta of non-inferiority margin (δ_{safety}) 8% for the safety endpoints, the hypotheses can be rewritten as:

H_0: $\pi_{Wingman\_safety} \geq 13.0\%$

H_A: $\pi_{Wingman\_safety} < 13.0\%$

Assume that the Wingman device has the same success rate and the major adverse event rate as the historical control and further assume that the one-sided type I error rates for the efficacy and safety endpoints are both 0.05. An effective sample size of 80 subjects is needed achieve a power of at least 80% for the efficacy and safety endpoints. To account for a loss of follow up rate of approximately 5%, total enrollment of 85 subjects is required.

1.5 Randomization

This is a non-randomized study.

2 ENDPOINT DEFINITIONS

2.1 Primary Efficacy Endpoint

Successful CTO Crossing – While using the Wingman device, successful CTO crossing is identified by successful guidewire placement in the distal true lumen confirmed by angiography with no clinically significant perforations.

All of the angiographic films obtained from this study will be reviewed by an independent core lab. Information from their angiographic review will be recorded on CRFs and tabulated for endpoint analysis. Angiographic review will include assessments of: lesions lengths, occlusion lengths, reference vessel diameter, calcification severity, successful CTO crossing, perforation and dissection.

In the event angiographic films are unavailable for assessment by the core lab, site-reported visual assessments will be used for analysis.

2.2 Secondary Efficacy Endpoints

- Lesion success, defined as attainment of <50% final residual stenosis of the target lesion using any percutaneous method.
- Procedure success, defined as device success and the absence of in-hospital MAEs, clinically significant perforation, clinically significant embolization or Grade C or greater dissection not resolved by visual estimate.
- Evaluation of total procedural and fluoroscopic time and contrast volume.
- Evaluation of procedure time associated with use of the investigational device.
- Evaluation of utility of ancillary device in addition to investigational device.

The angiographic elements of secondary efficacy endpoints will be assessed by an independent core laboratory and the MAE elements adjudicated by an independent CEC. In the event angiographic films are unavailable for assessment by the core lab, site-reported visual assessment will be used for analysis.

2.3 Exploratory Efficacy Endpoints

There are no exploratory efficacy endpoints.

2.4 Safety Endpoints

Primary Safety – No evidence of significant in-hospital or 30-day MAEs. No evidence of clinically significant perforation[1], clinically significant embolization or ≥Grade C dissection[1] after Wingman CTO crossing after Wingman CTO crossing and prior to adjunctive interventions, confirmed by angiography.

The components of the composite primary safety endpoint include:

- Major Adverse Events (MAEs) defined as death, unplanned target limb major amputation, and emergent target vessel revascularization.
- Clinically significant perforation defined as all perforations requiring intervention (e.g., covered stent, bypass or other surgery).
- Clinically significant embolization defined as those events that result in distal ischemia (e.g., occlusion of run-off vessel resulting in pain or foot discoloration) and/or requires rescue intervention.
- Grade C Dissection or greater with a minimum of a dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

The components of the primary safety endpoints will be adjudicated by an independent CEC with angiographic elements assessed by an independent core laboratory.

[1] That occur from study device, as adjudicated by the CEC. This would not include perforations or grade C dissections that occur before the use of the study device or those that occur after use of a commercially available therapeutic device (e.g. from atherectomy)

3 ANALYSIS POPULATIONS

3.1 Intention-To-Treat Population

The subject is enrolled in the study once informed consent has been obtained. If the subject has provided informed consent but has not met one of the criteria for inclusion into the study, they will be considered a screen failure.

Modified Intention to Treat (mITT) Population: The modified intention to treat (mITT) population will include all consented subjects who are exposed to the investigational device. Subjects who give consent but are not exposed to the investigational device or do not undergo the procedure will not be included in this population. The primary study endpoints will be evaluated in the mITT population.

The study visit flow is as follows:

Activity	Visit 1 (Baseline Evaluation) [a]	Visit 2 [a] (Index Procedure through Discharge)	Visit 3 (Follow-Up Evaluation) [e]
Eligibility Screening	X		
Informed Consent	X		
History and Physical Examination of target limb[f]	X		
Vital Signs [b]	X	X	
Ankle-Brachial or Toe-Brachial and Rutherford Assessments	X	X	X
Medication History and Review	X		
Peripheral Arterial Disease/CTO Confirmation [c]	X		
Laboratory Tests [d]	X		
Interventional Procedure and Angiography		X	
Adverse Experience Assessment		X	X
Device Accountability		X	
Protocol Deviations	X	X	X

[a] Visit 1 and Visit 2 study procedures may be conducted during one study visit, permitting that Visit 1 procedures have been performed within the past 90 days and are completed prior to the start of the interventional procedure. Urine pregnancy tests will also be conducted as necessary during the baseline evaluation per local requirements.

[b] Blood pressure, heart rate, respiratory rate, and weight.

[c] Confirmation of an occluded artery ≥ 2.0 mm in diameter requiring intervention based on contrast, CT or MR angiography.

[d] As per pre-interventional catheterization laboratory standard procedures.

[e] Visit will occur 30 days (+/- 7 days) post-interventional procedure.

[f] Existence of gangrene, tissue deficit, blue toe syndrome or any evidence of acute ischemia in low limb.

Missing data will not be imputed. However, a tipping point sensitivity analysis on the primary endpoints will be done.

3.2 Per Protocol Population

The per protocol population will include all enrolled subjects that meet the eligibility criteria, are exposed to the investigational device, undergo the index procedure and complete the 30-day follow up visit.

3.3 Safety Population

The safety population is the same as the mITT population for this study.

4 STATISTICAL ANALYSES

4.1 Baseline Characteristics

Demographic and baseline clinical and disease characteristics will be summarized in tables. For continuous variables, the summary will include number, mean, standard deviation, median, minimum, and maximum. Summaries for categorical variables, the number, and percent of subjects in each category will be calculated.

Procedural data will be summarized in tables including information on laboratory analysis, device and techniques, characteristics of the vessel and anticipated treated region, crossing attempts made with standard guidewire and study device, therapeutic treatments employed, device information / accountability.

Vital signs measures and ankle-brachial index will be summarized by study visit. Adverse events on the procedure day and within 30 days after the procedure will be summarized by tabulating the number of percentages of patients experiencing each event. Device and procedure related adverse events will be summarized separately.

Patient data listings including demographic, baseline characteristics, safety data, adverse events, procedural data and endpoints will be provided.

4.2 Efficacy Analyses

Descriptive statistics of the primary efficacy endpoint (total number of CTOs, number and percentage of successful CTO crossings, one-sided 95% CI of the percentage) will be presented. The lower bound of the one-sided 95% CI will be compared to the performance goal of 70.7%.

Summary statistics will be presented for procedural and fluoroscopic time and contrast volume and other secondary endpoints. The summary will include number, mean, standard deviation, median, minimum, maximum, as well as the two-sided 95% CI of the mean and box plots for non-normally distributed data.

4.3 Safety Analyses

Number and percentage of in-hospital and 30-day major adverse event and the one-sided 95% CI will be presented. The upper bound of the one-sided 95% CI will be compared to the performance goal of 13.0%.

Number and percentage of subjects having 30-day MAEs, device successes, lesion successes, procedure successes and subjects having clinically significant perforation, and the corresponding two-sided 95% CIs will be presented.

4.4 Poolability Analyses

Poolability of data across clinical study sites is justified on a clinical basis (i.e. all study sites use the same protocol) the sponsor monitors the site for protocol compliance, and the data gathering instruments are identical. The Food and Drug Administration (FDA) also requires a statistical assessment of poolability. This is done by comparing the baseline characteristics across study sites. For categorical baseline variables, such as sex, a generalized Fisher's exact test or equivalent test will be used and for quantitative variables, parametric or non-parametric analysis of variance (general linear models or an equivalent procedure) will be used.

The above statistical analyses do not result in an impediment to pooling, but rather assess the balance of baseline covariates across study sites. If any baseline covariate is found to be statistically significant by this process, multivariate analyses will be done to determine if imbalance affected study outcome. This is done by using both the variable found out of balance and study site as possible covariates.

It may be necessary to combine two or more low enrolling study sites into pseudo-sites to allow these analyses. Sites with fewer than 6 subjects will be ranked by enrollment low to high. Starting from the lowest enrollment sites, sites will be combined into a pseudo sites until the combined size reaches the median enrollment among all sites. This process will be repeated until all resulting sites have enrollment equal to or greater than 6 subjects. This will be done in a manner to preserve the structure of the study and prevents bias.

Baseline characteristics to be considered as possible covariates are as following:

- Age

- Gender
- Coronary artery disease
- Chronic obstructive pulmonary disease
- Myocardial infarction
- Hyperlipidemia
- Cerebrovascular accident
- Hypertension
- Diabetes mellitus
- History of tobacco use
- History of peripheral vascular disease
- Rutherford Category
- ABI/TBI

If there are relatively few missing data points (e.g., <10%) for a given variable, a simple sex-specific imputation using the mean (for continuous variables) or median (for dichotomous or categorical variables) of the non-missing values will be done. If there are >10% missing, the variable will be excluded from the imputation analysis.

Poolability analysis will also be performed on the primary endpoints comparing across sites after adjusting for covariates difference. Logistic regression models will be utilized to include unbalanced covariates and site as an independent variable and the study outcome as dependent variable to assess outcome difference. If the p-value of site effect is less than 0.10, further analyses will be undertaken to investigate the imbalance of the study outcome.

4.5 Subgroup Analyses

Subgroup analyses will be conducted for gender and diabetes mellitus status. Subgroup analyses of various endpoints such as crossing success, perforation, dissection and other adverse events may also be conducted. Analysis groups may include: guidewire tip load; access site; lesion calcification; lesion length and type of proximal stump.

4.6 Missing or Incomplete Data

Missing endpoint data will not be imputed. However, a tipping point sensitivity analysis on the primary endpoints will be done.

5 DESCRIPTION OF PLANNED TABLES, LISTINGS AND FIGURES

A detailed description of Tables, Listings and Figures (TLF) will be provided in a separate Mock TLF document.

6 REFERENCES

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[6] Saket R and Razavi M and Padidar A and Kee S and Sze D and Dake M. Novel Intravascular Ultrasound-Guided Method to Create Transintimal Arterial Communications: Initial Experience in Peripheral Occlusive Disease and Aortic Dissection. *Journal of Endovascular Therapy.* 2004:11;274-280.

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[10] Pigott JP and Davis T et al. A Multicenter Experience Evaluating Chronic Total Occlusion Crossing with the Wildcat Catheter (the CONNECT study). *J Vasc Surg* 2012:56:1615-21.

[11] Bosiers M and Dawkins KD, et al. Revascularization of lower extremity chronic total occlusions with a novel intraluminal recanalization device: results of the ReOpen study. *J Endovasc Ther*. 2014 Feb;21(1):6170. doi: 10.1583/124083R.1.