# Clinical Study Protocol

## A Prospective, Multicenter, Single-arm Investigation of the Ringer Perfusion Balloon Catheter (Ringer PTCA Study)

**Study Number: ST3170**

**Revision: E**

**21 March 2023**

Vascular Solutions LLC
(a subsidiary of Teleflex, Inc.)
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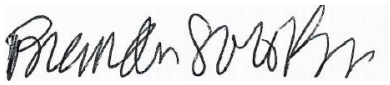
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## Principal Investigator Signature

I have read the clinical study protocol and agree to adhere to the requirements of this protocol in accordance with the ICH guidelines for good clinical practices, ISO 14155, and applicable FDA regulations.

**Printed Name:** _____ **Site #:** _____

**Signature:** _____ **Date:** _____

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| | |
|---|---|
| Teleflex® | **CLINICAL STUDY PROTOCOL SYNOPSIS**<br>**RINGER PTCA STUDY**<br>**Teleflex Study Number: ST-3170** |
| **Study Title** | A prospective, multicenter, single-arm investigation of the Ringer Perfusion Balloon Catheter (Ringer PTCA Study) |
| **Identifying Regulatory Numbers** | FDA IDE number – G200321<br>Canada ITA number – 324526<br>Clinicaltrials.gov – NCT04862689 |
| **Study Objective** | The primary objective of this study is to demonstrate safe and effective use of the Ringer perfusion balloon catheter for dilatation/pre-dilatation of coronary stenoses during percutaneous coronary intervention (PCI). The secondary objective is to demonstrate maintenance of coronary blood flow distal to the inflated Ringer device thereby enabling prolonged balloon inflation. The data captured in this study will be used to support a future marketing application for the Ringer perfusion balloon catheter. |
| **Device Description** | The Ringer perfusion balloon catheter is a rapid-exchange catheter with a spiral-shaped inflatable balloon on the distal end and a wire lumen for delivery over a ≤ 0.014" guidewire. The inflated spiral balloon approximates a hollow cylinder. Radiopaque markers at the proximal and distal end of the balloon facilitate visualization and intravascular placement of the catheter prior to inflation. The catheter shaft has positioning marks located at 95 cm (single mark) and 105 cm (double mark) from the distal tip. |
| **Device Indication** | The Ringer perfusion balloon catheter is intended for use during percutaneous transluminal coronary angioplasty (PTCA) where the physician desires distal perfusion during prolonged balloon inflation. |
| **Study Design** | The investigation is a prospective, multicenter, observational, single-arm clinical study.<br>The patient will be considered enrolled in the study when there is an attempt to deploy the Ringer perfusion balloon catheter (Ringer catheter enters guiding sheath). Subjects will undergo follow-up evaluations during the procedure and at hospital discharge. After the final follow-up assessment, subjects will exit from the clinical study and continue to be followed by their physician per standard of care. |
| **Number of Sites & Subjects** | The study will be conducted in up to 4 - 10 investigational sites in the US and Canada and will enroll up to 60 subjects. |

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| **Sample Size Justification** | The number of subjects (N=60) is based upon precision of estimation in this single-arm study. The observed success rate for the primary efficacy endpoint is anticipated to be in excess of 90%, and hence a sample size of 60 subjects treated with the Ringer device results in a standard error of less than 4%, which is sufficient for reasonable estimation. As the primary efficacy endpoint is based on procedural characteristics, this sample size is not impacted by subject attrition; additionally, higher success rates will produce correspondingly smaller standard errors and hence the cited value of 4% can reasonably be regarded as an upper bound. |
| **Study Population** | The population for this study is adult subjects clinically indicated for non-emergent percutaneous coronary intervention (PCI) as a stand-alone procedure or following non-emergent diagnostic angiography performed during the same procedure. |
| **Primary Efficacy and Safety Endpoint** | The primary efficacy endpoint is device procedural success consisting of:<br>• Successful delivery of the Ringer Perfusion Balloon Catheter to and across the target lesion<br>• Successful inflation and deflation with the Ringer Perfusion Balloon Catheter (and subsequent removal)<br>• No vessel perforation, no flow-limiting vessel dissection, no reduction in TIMI flow from baseline, and no clinically significant arrhythmias requiring medical treatment or device intervention following dilatation with the Ringer perfusion balloon catheter<br>• Achievement of a final TIMI flow grade of 3 at the conclusion of the PCI procedure for the lesion.<br>The primary safety endpoint will evaluate the occurrence of clinically relevant events during prolonged balloon inflations consisting of:<br>• Vessel perforation, flow-limiting vessel dissection, reduction in TIMI flow from baseline, and clinically significant arrhythmias requiring medical treatment or device intervention following dilatation with the Ringer perfusion balloon catheter<br>• Freedom from major cardiac adverse events (MACE) through hospital discharge or 30 days, whichever comes first. |
| **Secondary Endpoints** | Secondary endpoints are:<br>Efficacy:<br>• Successful PCI defined as: final residual stenosis ≤20% diameter stenosis (in-stent) or ≤50% diameter stenosis (stand-alone balloon) by visual angiographic estimation and freedom from MACE at hospital discharge. |

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| | • Maintenance of TIMI-2 or -3 flow into distal coronary bed during Ringer inflation.<br><br>Safety:<br><br>• Tolerance of at least one Ringer inflation greater than one minute (prolonged inflation) at target site (measured with symptoms, ECG, hemodynamics) |
| **Study Eligibility Criteria** | *Inclusion Criteria*<br><br>Subjects must meet all the following inclusion criteria:<br><br>1. Male and female subjects >18 years of age.<br>2. Patients undergoing clinically indicated non-emergent PCI as a stand-alone procedure or in combination with diagnostic angiography during the same procedure.<br>3. Patients with one or two target lesions planned during the index PCI, with one lesion identified as the study target lesion prior to initiating any PCI.<br>4. Study target lesion characteristics: a) native de-novo coronary stenosis of at least 70% visually estimated stenosis, or at least 50% visually estimated stenosis and shown to be physiologically significant by flow-mediated criteria (FFR <0.80, IFR <0.91); b) estimated reference vessel diameter 2.0-4.5mm; c) lesion length <25mm; d) calcification not greater than mild.<br>5. Per investigator judgement, the patient may benefit from distal perfusion during balloon inflation. Examples include but are not limited to: (i) LV systolic dysfunction with LVEF<50% by any modality; (ii) a territory subtended by the target vessel downstream from the target lesion that is estimated to be in excess of 25% of viable LV mass; (iii) prior hemodynamic or electrical instability during intervention on the target lesion; (iv) the potential to avoid placement of a coronary stent if a stent-like result can be achieved through prolonged balloon inflation.<br>6. Female subjects of childbearing potential must have a negative pregnancy test per standard of care for PCI and be practicing contraception<br>7. Informed consent provided.<br><br>*Exclusion Criteria*<br><br>Subjects must not meet any of the following exclusion criteria:<br><br>1. Hemodynamic or arrhythmic instability within 48 hours or a myocardial infarction within 72 hours of PCI.<br>2. More than 2 lesions planned during index PCI.<br>3. Procedural complication developing prior to PCI of study target.<br>4. Ejection fraction (EF) <25%. |

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| | |
|---|---|
| | 5. Creatinine clearance (Cr-Cl) <25 mg/dL.<br>6. Baseline flow at study target <TIMI-2. |
| **Study Sponsor** | Vascular Solutions LLC (a subsidiary of Teleflex, Inc.)<br>6464 Sycamore Court North<br>Minneapolis, MN 55369<br>USA<br><br>Christopher E. Buller, MD<br>Medical Director<br>Clinical and Medical Affairs<br>Telephone: +1 763-656-4335<br><br>Chris.buller@teleflex.com |
| **Angiographic Core Lab** | TBD |

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| Abbreviations | Description |
|---|---|
| ADE | Adverse device effect |
| AE | Adverse event |
| CABG | Coronary artery bypass graft |
| CEC | Clinical events committee |
| CFR | Code of federal regulations (U.S.) |
| CRF | Case report form |
| (e)CRF | (electronic) case report form |
| CRO | Contract Research Organization |
| CV | Curriculum vitae |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration (U.S.) |
| GCP | Good clinical practice |
| GUSTO | Global Use of Strategies to Open Occluded Coronary Arteries |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IDE | Investigational Device Exemption |
| IFU | Instructions for use |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| MACE | Major cardiac adverse event |
| MI | Myocardial infarction |
| PBI | Prolonged balloon inflation |
| PCI | Percutaneous coronary intervention |
| PI | Principal Investigator |

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| Abbreviations | Description |
|---|---|
| PTCA | Percutaneous transluminal coronary angioplasty |
| REB | Research Ethics Board |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| TIMI | Thrombolysis in myocardial infarction |
| UADE | Unanticipated (serious) adverse device effect |

# 1.0 INTRODUCTION

Percutaneous coronary intervention (PCI), also called coronary angioplasty or percutaneous transluminal coronary angioplasty (PTCA), is a minimally invasive non-surgical technique used to treat blocked or stenosed coronary arteries by allowing unobstructed blood flow to the myocardium. It is estimated that over 1 million PTCA procedures are performed annually in the United States, and over 3 million PTCA procedures performed worldwide. PTCA balloon catheters are specifically intended for balloon dilatation of a hemodynamically significant coronary artery or bypass graft stenosis in patients evidencing coronary ischemia for the purpose of improving myocardial perfusion, treatment of acute myocardial infarction, treatment of in-stent restenosis (ISR) and/or post-deployment stent expansion in PTCA procedures.

Distal ischemia is a risk associated with the use of prolonged balloon inflation (PBI) in the coronary and peripheral arteries. The Ringer perfusion balloon catheter (Ringer catheter) is a perfusion balloon catheter and can potentially mitigate the problem of distal ischemia by allowing blood flow through the device while the balloon is inflated. For example, the Stack perfusion balloon catheter (P810046, originally approved March 3, 1982) has a successful history of use in the coronary vasculature, and it carries an indication for use during PTCA procedures where a physician desires distal blood perfusion. Unfortunately, due to their limited market share, perfusion balloon catheters are no longer marketed, and physicians are left with standard PTCA balloons for PBI.

The Ringer catheter is intended to fill this gap in the market by providing a perfusion balloon catheter. Like the Stack perfusion balloon catheter, the Ringer perfusion balloon catheter is intended to provide distal blood perfusion during prolonged balloon inflations. Unlike the Stack device, the Ringer does not require removal of the coronary guidewire in order to achieve perfusion. This gives Ringer potential advantages in circumstances where maintenance of distal wire position is desired, such as very long lesions, diffuse disease, severe tortuosity, major bifurcations, or other circumstances when restoring distal wire position may be technically difficult or radiation/contrast demanding.

As an additional example, the Emerge PTCA dilatation catheter (K113220, originally approved March 22, 2012) is indicated for pre-dilatation or dilatation in the stenotic portion of a coronary artery or bypass graft stenosis (≥70% stenosis), for the purpose of improving myocardial perfusion and for the post-delivery expansion of balloon expandable stents (bare metal and drug-eluting).

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# 2.0 REGULATORY CLASSIFICATION

The Ringer catheter is investigational and does not currently have regulatory market approval inside or outside the U.S. The data captured in this study will be used to support a future marketing application for the Ringer catheter.

# 3.0 TREATMENT DESCRIPTION

## 3.1 Indications for Use

The Ringer perfusion balloon catheter is intended for use during percutaneous transluminal coronary angioplasty (PTCA) where the physician desires distal blood perfusion during prolonged balloon inflation.

## 3.2 Device Description

The Ringer perfusion balloon catheter (**Figure 1**) is a rapid-exchange catheter with a spiral-shaped inflatable balloon on the distal end and a wire lumen for delivery over a ≤ 0.014" guidewire. The inflated spiral balloon approximates a hollow cylinder (**Figure 2**). Radiopaque markers at the proximal and distal end of the balloon facilitate visualization and intravascular placement of the catheter prior to inflation. The catheter shaft has positioning marks located at 95cm (single mark) and 105cm (double mark) from the distal tip. The Ringer perfusion balloon catheter has been sterilized with ethylene oxide.

**Figure 1: Ringer Catheter**

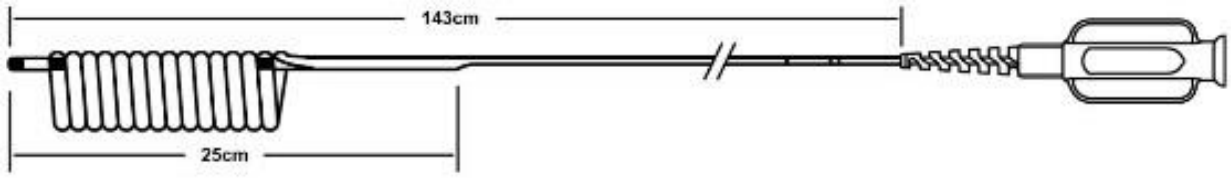
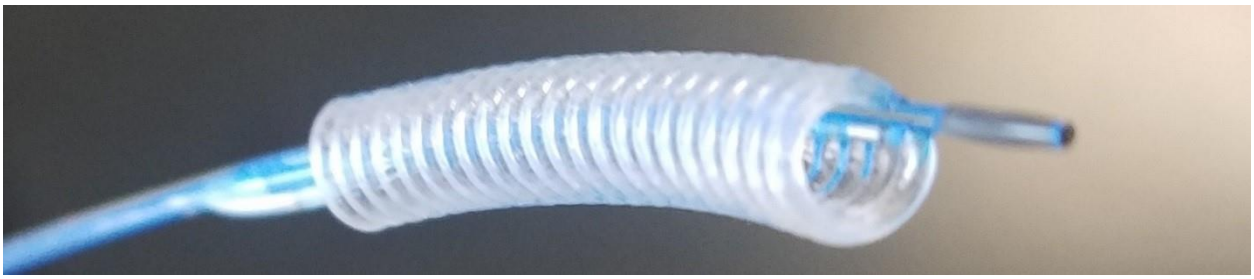



**Figure 2: Ringer Spiral-Shaped Balloon**

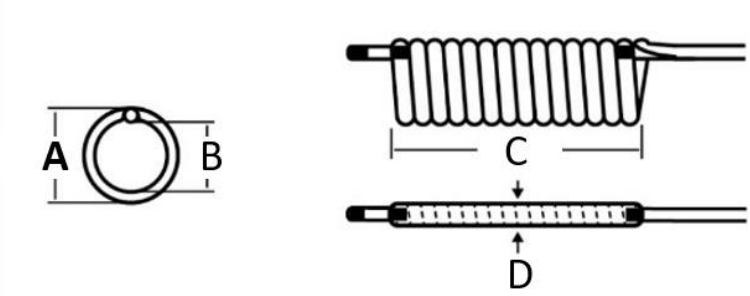


The Ringer catheter is available in eleven configurations summarized in **Table 1**.

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**Table 1: Ringer Catheter Configurations**

| Model | Balloon Outer Diameter | Balloon Inner Diameter | Balloon Length | Crossing Profile |
|---|---|---|---|---|
| Units | "A" (mm) | "B" (in) | "C" (mm) | "D" (in) |
| 5870 | 2.0 | 0.025 | 20 | 0.050 |
| 5871 | 2.5 | 0.039 | 20 | 0.052 |
| 5872 | 2.5 | 0.039 | 30 | 0.052 |
| 5873 | 3.0 | 0.059 | 20 | 0.054 |
| 5874 | 3.0 | 0.059 | 30 | 0.054 |
| 5875 | 3.5 | 0.079 | 20 | 0.056 |
| 5876 | 3.5 | 0.079 | 30 | 0.056 |
| 5877 | 4.0 | 0.099 | 20 | 0.058 |
| 5878 | 4.0 | 0.099 | 30 | 0.058 |
| 5879 | 4.5 | 0.119 | 20 | 0.060 |
| 5880 | 5.0 | 0.139 | 20 | 0.062 |




### 3.3 Principle of Operation / Mechanism

The Ringer catheter is backloaded onto a guidewire through the rapid-exchange lumen and advanced into the vasculature. The Ringer catheter has radiopaque marker bands positioned proximal and distal to the outer edges of the balloon to visualize the position of the balloon in the desired vasculature. Once the Ringer catheter is positioned in the desired location, the balloon is inflated by injecting a mixture of saline and contrast through the device hub, stainless steel hypotube and nylon inflation lumen. The balloon, which is tightly wrapped around the catheter shaft (inclusive of the inflation lumen plus rapid-exchange lumen), inflates to create a coiled hollow-tube that dilates the vessel while allowing blood to flow through the lumen of the balloon. The inflated balloon does not fully occlude the vessel, allowing distal perfusion through the lumen of the balloon. The Ringer catheter also accommodates the use of interventional devices while the balloon is inflated.

## 4.0 OBJECTIVE

The primary objective of this study is to demonstrate safe and effective use of the Ringer perfusion balloon catheter for dilatation/pre-dilatation of coronary stenoses during percutaneous coronary intervention (PCI). The secondary objective is to demonstrate maintenance of coronary blood flow distal to the inflated Ringer device thereby enabling prolonged balloon inflation. The data captured in this study will be used to support a future marketing application for the Ringer catheter.

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# 5.0 STUDY POPULATION

The population for this study is adult subjects clinically indicated for non-emergent percutaneous coronary intervention (PCI) as a stand-alone procedure or following non-emergent diagnostic angiography performed during the same procedure.

# 6.0 ENDPOINTS

## 6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is demonstration of the Ringer Perfusion Balloon Catheter procedural success during prolonged balloon inflations consisting of:

- Successful delivery of the Ringer Perfusion Balloon Catheter to and across the target lesion
- Successful inflation and deflation with the Ringer Perfusion Balloon Catheter (and subsequent removal)
- No vessel perforation, no flow-limiting vessel dissection, no reduction in TIMI flow from baseline, and no clinically significant arrhythmias requiring medical treatment or device intervention following dilatation with the Ringer Perfusion Balloon Catheter
- Achievement of a final TIMI flow grade of 3 at the conclusion of the PCI procedure for the lesion.

## 6.2 Primary Safety Endpoint

The primary safety endpoint will evaluate the occurrence of clinically relevant events during prolonged balloon inflations consisting of:

- Vessel perforation, flow-limiting vessel dissection, reduction in TIMI flow from baseline, and clinically significant arrhythmias requiring medical treatment or device intervention following dilatation with the Ringer Perfusion Balloon Catheter
- Freedom from major cardiac adverse events (MACE) through hospital discharge or 30 days, whichever comes first.

## 6.3 Secondary Endpoints

Secondary endpoints include:

Efficacy:

- Successful PCI defined as: final residual stenosis ≤20% diameter stenosis (in-stent) or ≤50% diameter stenosis (standalone balloon) by visual angiographic estimation and freedom from MACE at hospital discharge.
- Maintenance of TIMI-2 or -3 flow into distal coronary bed during Ringer inflation.

Safety:

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- Tolerance of at least one Ringer inflation greater than one minute (prolonged inflation) at target site (measured with symptoms, ECG, hemodynamics).

# 7.0 STATISTICAL METHODS

### 7.1.1 Analysis Datasets

All analyses will be conducted under the principles of intent-to-treat, using the full analysis set (FAS) as defined in ICH E9 (Statistical Principles for Clinical Trials). Primary analyses will include all available data on all enrolled subjects.

### 7.1.2 General Principles

Standard summary statistics will be calculated and reported; for continuous variables, statistics will include means, standard deviations, medians and ranges or interquartile ranges. Categorical variables will be summarized in frequency distributions. All statistical analyses will be performed using SAS (version 9.4 or higher, SAS Institute Inc. Cary, NC), R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical or graphical software.

### 7.1.3 Analysis of Primary Endpoint

The primary efficacy endpoint is defined as described in **Section 6.1**. This endpoint will be assessed for each subject and presented as a proportion of successes and failures. The primary safety endpoint is defined as described in **Section 6.2** and will be adjudicated by the Clinical Events Committee (CEC). This endpoint will be tabulated and reported as the number and percentage of subjects experiencing at least one safety event as well as the total number of such events, with the primary assessment based on the number of subjects experiencing an event. Additionally, to provide formal statistical conclusions on the error of estimation for both primary endpoints, each will be presented with its corresponding two-sided 95% confidence interval, calculated by the exact (Clopper-Pearson) method.

### 7.1.4 Analysis of Secondary Endpoints

Secondary endpoints will be summarized and tabulated according to the general principles in **Section 7.1.2**.

### 7.1.5 Safety Analysis

Summary tables and listings will be provided for all reported adverse events (AEs), which will additionally be reported by seriousness and relatedness. Such summaries will be comprised of the number and percentage of subjects with an AE and the total number of such events. As in **Section 7.1.3**, the proportion of subjects with events will be considered primary for analysis of AEs.

### 7.1.6 Number of subjects (Sample Size) and Justification

The study will enroll 60 subjects based upon precision of estimation in this single-arm study. This sample size, as well as the anticipated success rate for the primary efficacy endpoint, is based upon regulatory studies of comparable products in a similar patient population, notably the Emerge PTCA Dilatation Catheter (Boston Scientific, US: K130391, Canada Medical Device

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License Number: 90397), which also enrolled 60 subjects. The primary efficacy endpoint is defined as device procedural success, consisting of successful delivery, inflation, deflation, and withdrawal of the Ringer device. The observed success rate for the endpoint is anticipated to be in excess of 90%, and hence a sample size of 60 subjects treated with the Ringer device results in a standard error of less than 4%, which is sufficient for reasonable estimation. As the endpoint is based on procedural characteristics, this sample size is not impacted by subject attrition; additionally, higher success rates will produce correspondingly smaller standard errors and hence the cited value of 4% can reasonably be regarded as an upper bound.

# 8.0 STUDY DESIGN

## 8.1 Overall Design

The investigation is a prospective, multicenter, single-arm clinical study.

## 8.2 Number of Sites & Subjects

The study will be conducted in 4 to 10 investigational sites in the US and Canada and will enroll up to 60 subjects. The study Sponsor and CRO will manage sites so that no single site enrolls more that approximately one-third of the total study enrollment, or 20 subjects.

## 8.3 Study Duration

Enrollment is expected to take approximately 12 months. Each study subject will actively participate in the study through hospital discharge. The overall study duration from first IRB/REB approval to data analysis and final report is expected to be approximately 15 months.

## 8.4 Subject Eligibility Criteria

### 8.4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Male and female subjects >18 years of age.

2. Patients undergoing clinically indicated non-emergent PCI as a stand-alone procedure or in combination with diagnostic angiography during the same procedure.

3. Patients with one or two target lesions planned during the index PCI, with one lesion identified as the study target lesion prior to initiating any PCI.

4. Study target lesion characteristics: a) native de-novo coronary stenosis of at least 70% visually estimated stenosis, or at least 50% visually estimated stenosis and shown to be physiologically significant by flow-mediated criteria (FFR <0.80, IFR <0.91); b) estimated reference vessel diameter 2.0-4.5mm; c) lesion length <25mm; d) calcification not greater than mild.

5. The patient has, in the judgement of the operator, the capacity to benefit from prolonged inflation enabled by distal perfusion during balloon inflation. Examples include but are not limited to: (i) LVEF <50% by any modality (ii) a territory subtended by the target vessel downstream from the target lesion that is estimated to be in excess of 25% of LV mass

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(iii) prior hemodynamic or electrical instability during intervention on the target lesion (iv) the potential to avoid placement of a coronary stent if a stent-like result can be achieved through prolonged balloon inflation.

6. Female subjects of childbearing potential must have a negative pregnancy test per standard of care for PCI and be practicing contraception

7. Informed consent provided.

### 8.4.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. Hemodynamic or arrhythmic instability within 48 hours or a myocardial infarction within 72 hours of PCI.
2. More than 2 lesions planned during index PCI.
3. Procedural complication developing prior to PCI of study target.
4. Ejection fraction (EF) <25%.
5. Creatinine clearance (Cr-Cl) <25 mg/dL.
6. Baseline flow at study target <TIMI-2.

# 9.0 STUDY METHODOLOGY

## 9.1 Screening

Screening is defined as the process of reviewing a patient's medical records against the study eligibility criteria to determine if the patient is potentially eligible to enroll in the study. It is expected that the medical records will contain adequate information to determine if a patient meets most of these criteria. If the Investigator (or designee) determines the patient meets all inclusion criteria and no exclusion criteria, they can be consented for study participation. If any criteria are not met prior to the procedure, the patient will be considered a screen failure and will be tracked on the Screen Failure Log.

## 9.2 Informed Consent

Prior to enrolling patients in this study, the site will be required to have an Institutional Review Board (IRB)/Research Ethics Board (REB) approved informed consent form (ICF). The contract research organization (CRO), if appliable, must approve any modifications made to the Sponsor's template ICF prior to IRB/REB submission. Written informed consent will be obtained from the patient prior to the subject's participation in the study. The Investigator (or authorized designee) will explain the nature of the planned treatment and objectives of the study to the patient, allowing adequate time for the patient to read and review the consent form and to ask questions. The patient and the Investigator (or authorized designee) will sign and date the ICF.

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The site will retain the original signed ICF in the subject's study records and will provide a copy of the signed ICF to the subject. The site will document the consent process (e.g., that the subject was consented, the date on which the consent was obtained, and that a copy of the signed ICF was given to the subject) in the subject's medical records. Subjects will be informed of any new information that may make him/her change their mind about staying in the study. Subjects may be asked to sign a new ICF if this occurs.

### 9.2.1 Vulnerable Population

The Sponsor is not anticipating enrollment of a vulnerable patient population (ref. ISO 14155:2011 section A.15).

## 9.3 Point of Enrollment & Numbering of Study Subjects

A patient will be considered enrolled as a study subject once the Ringer catheter enters the arterial sheath. The site staff assigns the lowest available subject number progressing sequentially for each enrolled subject (e.g., 001, 002, 003). As soon as possible after a subject is enrolled, a member of the site's study team will notify the CRO (or Sponsor, as applicable), preferably by an entry in the electronic data capture (EDC) system or via email notification. The Sponsor and/or CRO will manage sites so that no single site enrolls more than approximately one-fourth of the total study enrollment.

## 9.4 Schedule of Visits & Testing Requirements

**Table** outlines the visits, visit windows, and testing requirements at each evaluation time point.

**Table 2: Visits & Testing Requirements**

| Testing & Data Collection | Screening/baseline | PCI Procedure | | 18 to 24 Hours post-procedure or Hospital Discharge (whichever comes first) |
|---|---|---|---|---|
| | | Pre-Ringer Deployment | Ringer Deployment & Procedural Data | |
| ICF and opportunity for discontinuation | √ | | | |
| Pregnancy test | √ | | | |
| Inclusion and exclusion criteria | √ | √ | | |
| Angiographic imaging | | √ | √ | |
| TIMI flow | | √ | √ | |
| Demographics | √ | | | |
| Medical & surgical history | √ | | | |
| Cardiac medication review | | | | √ |
| Cardiac Troponin | √ | | | √ |
| Adverse event assessment | | | √ | √ |
| Device deficiency assessment | | | √ | |

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## 9.5 Subject Assessments & Study Procedures

Note: See **Section 14.0** for definitions of endpoint-related terms used in this section.

### 9.5.1 PCI Procedure: Pre-Ringer Deployment

Standard catheterization and angiographic procedures will be followed during this study.

### 9.5.2 PCI Procedure: Ringer Deployment & Procedural Data

The Ringer catheter will be deployed in subjects who meet the inclusion and exclusion criteria. Refer to the Ringer catheter IFU for instructions on the clinical and deployment procedure.

**Note:** *The Ringer perfusion balloon catheter is not intended for treatment of in-stent restenosis or expansion or delivery of a stent.*

PCI procedural data will be collected on the electronic Case Report Forms (eCRFs) including:

- Procedural durations including start/end times
- Target vessel characteristics
- Target lesion characteristics
- Access site location(s)
- Number of Ringer catheters used
- Model of Ringer catheter(s) used during procedure
- Number of Ringer catheter deployment attempts
- Successful deployment of Ringer at lesion site
- Successful withdrawal of Ringer from guide catheter
- Ringer catheter inflation duration
- Maximum Ringer catheter balloon pressure (atm)
- Air Kerma (Gy) and total fluoroscopy time
- Procedure-related medications
- TIMI flow while Ringer is inflated
- Devices advanced through the inflated Ringer (if any)

### 9.5.3 18 to 24 Hours or Hospital Discharge to 30-days (whichever comes first)

The following evaluations and assessments will be performed 18-24 hours post-procedure or directly prior to discharge, whichever comes first:

- Cardiac medication review (refer to **Section 14.0** for definition).
- Adverse event assessment (device-related versus no device-related, MACE).
- Blood test: cardiac troponin (cTn)

Subjects may exit from this study at the conclusion of this visit unless for some medical reason the hospitalization continues. These subjects will then exit the study at discharge or at 30-days post-procedure whichever comes first. Exit and completion of a subject from the study will be

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documented in the Study Completion eCRF. Subjects will continue to be followed by their physician per usual care.

#### 9.5.4 Early Withdrawal/Premature Discontinuation of Subjects

Subjects may be withdrawn early from the study for several reasons including:

- Subject death
- Subject request for withdrawal (withdrawal of consent)
- Investigator decision, to be fully documented
- Safety reasons, as determined by Investigator, IRB/REB, FDA, or Health Canada

The Study Completion eCRF will be used to document all subjects that successfully complete the study as well as all subjects that are discontinued from the study early. The reason for early discontinuation will be clearly described.

If a subject chooses to withdraw from the study and withdraws consent for disclosure of future information, no further evaluation(s) should be performed, and no additional data will be collected. The Sponsor may retain and continue to use any data collected prior to the withdrawal of consent.

# 10.0 MEASURES TO AVOID & MINIMIZE BIAS

The study has several measures that have been implemented to avoid and minimize bias including:

- Establishment of a Clinical Events Committee (CEC) to independently monitor safety and review and adjudicate AEs.
- Use of an independent angiographic core laboratory for systematic review of images removing any potential for Investigator bias.

## 10.1 Angiographic Core Laboratory

An angiographic core laboratory will be used to provide an unbiased assessment of angiographic imaging. The angiographic core laboratory will provide image acquisition and processing instructions to the sites (Angiographic Core Laboratory Guidelines). The angiographic core laboratory will follow its own Charter or similar procedure to systematize their image review in compliance with the study protocol.

# 11.0 ADVERSE EVENTS

## 11.1 Adverse Event (AE) Definitions

Refer to **Section 14.0** for AE definitions.

The following are <u>not</u> considered AEs for this study:

- Any condition that is recorded as pre-existing on the Demographics & Medical History eCRF, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.

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- Any normal expected symptoms associated with PCI unless the event involves a clinically significant change in severity or duration of symptoms or requires clinical intervention that is different from ordinary postoperative care. The following are examples of the normal responses to all PCI procedures and are not considered AEs:
  - Transient arterial spasm resolving spontaneously OR with medication only.
  - Transient sinus bradycardia with heart rate ≥ 45 bpm, with no hemodynamic impact, and resolving spontaneously (Prophylactic placement and automatic activation of a cardiac pacer during this transient period does not constitute an intervention).
  - Minor discomfort or bruise at the arterial access place.
  - Small amount of bleeding at point of arterial access that does not result in a hematoma > 5 cm, need for a transfusion, or hemodynamic compromise.
  - Side effects of standard-of-care medications.

## 11.2 Adverse Event Collection & Documentation

Collection of AEs will start when subjects are enrolled and will be assessed and reported throughout the study. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a related serious AE (SAE) requiring immediate notification. All AEs will be followed until resolution or Investigator determination that the subject's condition is stable.

All reported AE will be documented on the AE eCRF. Copies of de-identified source documentation that contain significant information related to the event, such as progress notes, consultations, nurse's notes, operative reports and subject summaries, etc. may be requested by the Sponsor, CRO (if applicable), CEC and/or angiographic core lab as needed for evaluation and adjudication.

Device deficiencies of the Ringer catheter will also be collected. If a deficiency results in the subject experiencing any untoward medical occurrence, unintended disease or injury, or untoward clinical signs, these outcomes will be reported as an AE on an AE eCRF. Any malfunctioning Ringer catheters will be returned to the Sponsor by the Site for further evaluation.

In case of subject death, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the Sponsor or CRO (if applicable). Any other source documents related to the death should also be provided to the Sponsor or CRO (if applicable). If no source documents are available, the PI is required to describe the circumstances of the subject's death in written communication (e.g., letter, e-mail).

## 11.3 AE Reporting Timeframes

The Investigator is responsible for reporting SAEs to the IRB/REB in accordance with the IRB/REB's procedures. Unanticipated adverse device effects (UADEs) have special reporting requirements for both the Investigator and Sponsor, as described in 21 CFR 812.150:

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- **Investigator Report:** If a subject experience a UADE, the Investigator must notify the Sponsor and the reviewing IRB/REB as soon as possible, but no later than 10 working days after the Investigator first learns of the effect.
- **Sponsor Report:** UADEs will be reported to the FDA, all reviewing IRB/REBs, and participating Investigators as soon as possible, but no later than 10 working days after receiving notice of the UADE.

### 11.4 AE Relationship

The Investigator and the CEC will assess the relationship of the AE to the device treatment or procedure as follows:

- **Definitely:** The AE follows a strong temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure. This can include an AE that occurs after the study procedure.
- **Probably:** The AE follows a reasonable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, and the possibilities of other factors, such as underlying and concomitant illness, concomitant medications, or concurrent treatment can be excluded.
- **Possibly:** The AE follows a reasonable temporal sequence from receipt (or attempted receipt) of the device treatment or procedure and the possibility of device treatment or procedure involvement cannot be excluded. However, other factors such as underlying or concomitant illness, concomitant medications, or concurrent treatment are presumable.
- **Unlikely:** The AE has an improbable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, or it can be reasonably explained by other factors, including underlying or concomitant illness, concomitant medications, or concurrent treatment.
- **Not Related:** The AE has no temporal sequence to the interventional procedure, the device treatment, or any user handling, or it can be explained by other factors, including underlying disease or concomitant illness, concomitant medication, or concurrent treatment.

AEs adjudicated by the CEC as *definitely* or *probably* will be considered related AEs for data analytic purposes. Events adjudicated by the CEC as *possibly*, *unlikely* or *not related* will not be considered related AEs for data analytic purposes.

## 12.0 RISK/BENEFIT ANALYSIS

### 12.1 Potential Benefits of Study Participation

There are no guaranteed benefits from participation in this study; however, it is possible that use of the Ringer catheter may provide potentially lower risk of ischemia during prolonged balloon inflation given the facilitation of perfusion through the Ringer catheter balloon.

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## 12.2 Alternative Treatment

There is no obligation for a patient to take part in this study. The alternative option for prolonged balloon inflations is inflation with standard PTCA balloons which do not provide distal perfusion.

## 12.3 Potential Risks Associated with Study Participation

As with any interventional procedure, use of the study device during PCI involves some risks. The frequency and severity of AEs can vary, and may necessitate additional medical intervention, including surgery. The following potential risks or discomforts may be associated with the study device:

- Abrupt closure
- Angina or unstable angina
- Arrhythmias
- Arteriovenous fistula
- Cardiogenic shock
- Cardiac tamponade/pericardial effusion
- Coronary aneurysm
- Death
- Drug reactions, allergic reaction to contract medium
- Embolism
- Emergency surgical procedure
- Hemodynamic compromise
- Hemorrhage or hematoma
- Hypo/hypertension
- Infection
- Ischemia
- Myocardial infarction
- Percutaneous re-intervention
- Pseudoaneurysm (at the site of catheter insertion)
- Pyrogenic reaction
- Renal failure
- Respiratory insufficiency
- Restenosis of the dilated vessel
- Side branch occlusion
- Stent dislodgement
- Tamponade
- Thrombosis

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- Vessel dissection
- Vessel perforation
- Vessel spasm
- Vasovagal reactions
- Volume overload

Risks associated with the PCI procedure will be listed in the site's procedure consent form used per their standard of care.

Additional possible risks from the evaluations required during this study (but not directly related to the use of the Ringer catheter) include:

- Laboratory Testing Risks:

  For blood tests, a sample will be taken by inserting a needle into a vein in the arm. Some risks of this procedure include fainting, infection, bruising, formation of a blood clot, pain, and/or bleeding at the site of the needle puncture.

### 12.4 Methods to Minimize Risks

A risk analysis has been conducted and risks have been minimized or eliminated through appropriate design control and confirmed by pre-clinical bench and laboratory testing. To mitigate the risks above, Teleflex will work with interventional cardiologists trained specifically in PCI techniques, train all study personnel, and provide device labeling that contains precautions, warnings, and contraindications.

### 12.5 Risk-to-Benefit Rationale

The results from the risk analysis and risk mitigation measures support reasonable assurance of the safety and efficacy of the Ringer perfusion balloon catheter. Due to the similarity of the Ringer catheter to other marketed PTCA balloon catheters, procedural use is not expected to significantly change or increase risks, thereby supporting a clinical benefit to risk determination that is favorable for the Ringer catheter.

## 13.0 ADMINISTRATIVE PROCEDURES

### 13.1 Records & Reports

#### 13.1.1 Case Report Forms (CRFs)

A clinical trial database commonly referred to as an EDC system will be used to collect study-required data on eCRFs. The Principal Investigator (PI) at the site is responsible for ensuring the eCRFs are accurate and completed in a reasonable timeframe. The PI is required to review and approve the eCRF on the appropriate page(s) to verify the completeness, accuracy, and authenticity of the recorded data.

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### 13.1.2 Sponsor / CRO Study Records

The Sponsor and CRO (if applicable) are responsible for maintaining study records and reports per applicable ICH Good Clinical Practices (GCP), FDA regulations, ISO 14155, and applicable standard operating procedures and study specific plans (e.g., Monitoring Plan, Data Management Plan, Training Plan, and Statistical Analysis Plan).

### 13.1.3 Investigator Study Records

The Investigator will maintain the following accurate, complete, and current records relating to their participation in the study as follows:

- All significant correspondence that pertains to the investigation.
- Records of each subject's case history and exposure to the study device. Case histories include the eCRFs and supporting data including, for example, signed and dated ICFs (if applicable) and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records will include:
  - Documents evidencing the informed consent process. The case history of each individual will document that inclusion of the study was disclosed to the subject and whether the subject chose to discontinue study participation (per 21 CFR 50.24).
  - All relevant observations, including records concerning AEs effects (whether anticipate or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
  - A record of the exposure of each subject to the study device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates and reasons for each deviation from the protocol.
- Signed Investigator Agreements, financial disclosure agreements, Investigator signature pages from the protocol, and curriculum vitae (CV).
- IRB/REB approval documents including approval of the protocol, protocol amendments and ICF.

### 13.1.4 Investigator Reporting Requirements

Investigator reporting requirements are noted in **Table** below.

**Table 3: Investigator Reporting Requirements**

| Report | Submitted To | Description |
|---|---|---|
| Unanticipated Adverse Device Effects (UADE) | Sponsor/ CRO & IRB/REB | Notification within 10 working days after the Investigator first learns of the effect. |

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| Report | Submitted To | Description |
|---|---|---|
| Device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate | Sponsor/ CRO | Notification within 5 working days after the Investigator first learns of the device deficiency that might have led to an SAE. |
| Serious Adverse Events (SAE) | IRB/REB | Per IRB/REB reporting requirements. |
| Withdrawal of IRB/REB approval | Sponsor/ CRO | Notification within 5 working days of withdrawal. |
| Progress Report | Sponsor/ CRO & IRB/REB | Periodic report detailing the progress of the study, occurring at least annually. |
| Deviations from protocol (CFR 812.150) | Sponsor/ CRO & IRB/REB | **Emergency Use:** Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject).<br>**Other:** If the deviation affects scientific soundness of the study or the rights, safety, or welfare of the subject (and is not an emergency), prior approval must be obtained from Sponsor the reviewing IRB, and FDA when required. |
| Failure to obtain informed consent (informing subject/LAR/family of subject's inclusion in study and opportunity to discontinue) | Sponsor/ CRO & IRB/REB | Notification within 5 working days. |
| Final Report | Sponsor/ CRO & IRB/REB | Submitted within 3 months after termination or completion of the investigation. |

### 13.1.5 Record Storage & Retention

Refer to the Clinical Research Agreement (CRA) for trial data storage, access, and retention requirements.

## 13.2 Data Management

Correction of missing or unclear data will be requested as necessary throughout the study. The Sponsor or CRO (if applicable) may request additional information including source documentation as needed. The Sponsor or CRO will also be responsible for confirming the overall integrity of the data. Refer to the study-specific Data Management Plan for more details.

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## 13.3 Device Accountability and Storage

Investigators are required to maintain device accountability of the study devices (per 21 CFR 812.140(2)). All study devices will be labeled with reference and lot numbers, which will be recorded on the applicable eCRF when the device is used. Upon receipt of the study devices, the Study Coordinator or designee will inventory the devices and confirm receipt. As subjects are enrolled, the date of procedure, subject identifiers, and device disposition will be recorded on the eCRFs and Device Accountability Log. Sites will prevent use of investigational product for non-investigational procedures. The Ringer catheters must be stored according to the labeling, in a secure location to prevent unauthorized access or use, and will be promptly returned upon expiration, study completion, or termination.

## 13.4 Site Selection

Potential investigative sites are nominated for inclusion in the study based on their research history and expertise in PCI procedures. The Sponsor and CRO (if applicable) will further assess each potential site to ensure the Investigators and his/her staff meet the minimum following criteria:

- The site has an interventional cardiologist that can act as PI.
- The Investigators are qualified by experience and training.
- The site has adequate research support staff with the availability to fulfill the clinical study requirements specified in the protocol.
- The site has adequate access to patients undergoing PCI procedures.
- The site is not participating in another investigational study that is currently enrolling subjects with competing eligibility criteria; studies that have completed enrollment and are in the subject follow-up phase would not exclude the site from participation in this study.
- The Investigators are not on the FDA disqualified or debarred list.

## 13.5 Site Training

Training of the clinical site personnel will be the responsibility of the Sponsor and the CRO (if applicable). Site personnel will be trained per the study-specific Training Plan. All site personnel will undergo training prior to performing any study-related procedures. All training will be documented. Existing site personnel who have been delegated new tasks and new site personnel will undergo training as designated in the Training Plan.

## 13.6 Site Monitoring

This clinical study will be monitored according to a study-specific Monitoring Plan that complies with GCP. Monitors will assess for appropriate study conduct and data integrity, including review of eCRFs and parity checks with the source documentation, worksheets, and hospital charts. At a minimum, the ICF and the ICF process (inclusion in study and opportunity to discontinue), eligibility criteria, primary and secondary endpoint data, and adverse event data will be 100% monitored and compared to source documentation.

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## 13.7 Institutional Review Board (IRB)/Research Ethics Board (REB)

A central or institutional ("local") IRB/REB will review and approve this study for each participating site. The site must submit the protocol and ICF to the IRB/REB and forward a copy of the written approval to the Sponsor or CRO. The study identification (study number, protocol title, and version), documents approved (e.g., protocol, ICF), and the date of the review should be clearly stated on the IRB/REB approval documentation, and the approval must be signed by the IRB/REB. The site will not be activated to enroll subjects until a copy of written and dated approval has been received by the Sponsor or CRO and other applicable study activation requirements as outlined in the Monitoring Plan are complete. The site must submit any protocol or ICF amendments to the IRB/REB and is required to forward a copy of the written approval to the Sponsor or CRO. An IRB/REB approval of the amended document(s) must be obtained before implementation and before new subjects are consented to participate in the study using the amended ICF, if applicable. The IRB/REB should also be informed of any event likely to affect the safety of subjects or the conduct of the study. The ICF must be reviewed by the Sponsor prior to submission to the IRB/REB for approval.

## 13.8 Protocol Deviations

A protocol deviation is defined as a circumstance in which the Investigator or other site personnel did not conduct the trial according to the protocol, applicable laws/regulations, or any study agreements (e.g., Clinical Research Agreement or Investigator Agreement). Every attempt will be made to adhere to the protocol. However, should an Investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice will be given to the Sponsor or CRO as soon as possible, but no more than 5 working days from the date the emergency occurred. Except for an emergent circumstance, prior approval from the Sponsor and the IRB/REB is required for any change in, or deviation from, the protocol as such changes may affect the scientific soundness of the protocol or the rights, safety, and welfare of study subjects. Protocol deviations will be documented on the Protocol Deviation eCRF. Deviations are reportable to the Institution's governing IRB/REB during the annual reporting process, unless otherwise directed by the governing IRB/REB requirements. Repeated serious protocol deviations will be closely monitored by the Sponsor or CRO. If excessive deviations or a failure to reduce deviations is noted, the Sponsor reserves the right to suspend study enrollment or terminate the site from the study until a sufficient system is in place at the site to reduce further deviations (21 CFR 812.46(a)).

## 13.9 Protocol Amendments

Changes to the protocol must be documented in a formal protocol amendment prior to implementation in the study. Amendments to the protocol will be initiated by the Sponsor or CRO (if applicable) and must be approved by the IRB/REB prior to implementation at the site.

## 13.10 Study Termination

No formal statistical rule for early termination of this study for insufficient effectiveness of the study device is defined. The Sponsor reserves the right to terminate or suspend the study for valid

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scientific or business reasons, or reasons related to the protection of subjects (e.g., the discovery of an unexpected, significant, or unacceptable risk to subjects). If the study is terminated prematurely or suspended, the Sponsor will promptly inform all Investigators of the termination or suspension and the reason(s). The IRB/REB will also be informed, either by the Sponsor or Investigator, and provided with the reasons(s) for the termination or suspension. If applicable, regulatory authorities will be informed. The IRB/REB may choose to discontinue the study at any Site for which they granted approval if the research study is not conducted in accordance with the IRB/REB's requirements or the research study indicates unexpected serious harm to subjects.

### 13.11 Subject Confidentiality

All information and data sent to the CRO concerning a subject or their participation in this study will be considered confidential. The Sponsor, CRO (if applicable), Monitors, CEC, IRB/REB, and regulatory representatives will have access to these confidential files and have the right to inspect and copy all records pertinent to this study for data verification. All data used in the analysis and reporting of this study will be without identifiable references to a subject. Subject names and contact information will be available to the Sponsor, CRO, and Monitors during review of medical records. Subject names may be available to the core laboratory and the CEC as they review study-related radiographic images and source documentation. This information will be treated with adherence to professional standards of confidentiality. In addition, upon regulatory request, subject records shall be provided to U.S. regulatory agencies.

### 13.12 Statements of Compliance

This study is to be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, as defined in the following US and international standards for good clinical practice:

- International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6 (R2) (2016)
- U.S. Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 11, 50, 54 and 56 and 812) and HIPAA (45 CFR 164.508)
- ISO 14155: 2011

### 13.13 Study Contacts

Refer to the Sponsor Contact List for detailed contact information, including names, telephone numbers and email addresses for the Sponsor and CRO (if applicable).

## 14.0 DEFINITIONS

**Adverse device effect (ADE):** An adverse event (AE) related to the use of an investigational medical device. *[ISO 14155:2011(E)]*

- This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the

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investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device.

**Adverse event (AE):** Any untoward medical occurrence in a clinical investigation subject that does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. An untoward event that is related to the study device may be referred to as an Adverse Device Event. [*ref. ICH E6(R2) Good Clinical Practice: Consolidated Guidance*].

**Bleeding complications:** Bleeding complications will be defined according to the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) classification of severe, moderate, and mild bleeding events.

*Severe or life-threatening*: Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

*Moderate***:** Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

*Mild:* Bleeding that does not meet criteria for either moderate or severe bleeding.

**Cardiac death:** Any fatal event not attributable to a noncardiac cause.

**Cardiac medication:** Cardiac medications include:

- Antiplatelet medications such as aspirin, Clopidogrel, Prasurgrel, Ticlid, Ticagrelor
- Angiotensin converting enzyme (ACE) inhibitors
- Angiotensin receptor blockers (ARBs)
- Beta-blockers
- Calcium channel blockers
- Statins
- Other lipid lower agents
- Proton pump inhibitors
- Diuretics
- Anticoagulants
- Vasodilators

**Device deficiency:** Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *[ISO 14155:2011(E)]*

- Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

**Major adverse cardiac event (MACE):** Any serious adverse experience that includes death, target lesion revascularization, or post-procedural MI. Classification of an event as a MACE will

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be performed by the CEC. [*based on Academic Research Consortium definitions; ref. Garcia-Garcia 2018*]

**Myocardial infarction (MI):** Absolute rise in cardiac troponin (cTn) of ≥ 35 times upper reference limit (URL) from baseline, plus 1 (or more) of the following criteria;

- New significant Q waves (development of new Q waves ≥40 ms in duration and ≥1 mm deep in voltage in ≥2 contiguous leads)
- Flow-limiting angiographic complications
- New "substantial" loss of myocardium on imaging

[*based on Academic Research Consortium definitions; ref. Garcia-Garcia 2018*]]

**Serious adverse event (SAE):** Any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity. *[ref: ICH E6(R2) Good Clinical Practice: Consolidated Guidance]*

- Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

**Target lesion revascularization:** repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion [*based on Academic Research Consortium definitions; ref. Garcia-Garcia 2018*]

**Therapeutic Window:** The time period after onset of the event, based on available scientific evidence, within which the investigational product must be used or administered to have its potential clinical effect (diagnostic or therapeutic).

**TIMI:** Thrombolysis in myocardial infarction grading scale. [*TIMI Study Group, 1985*]

| | |
|---|---|
| **TIMI 0 - no perfusion** | There is no antegrade flow beyond the point of occlusion. |
| **TIMI I - penetration without perfusion** | The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence. |
| **TIMI II - partial perfusion** | The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel – e.g., the opposite coronary artery or the coronary bed proximal to the obstruction. |
| **TIMI III - complete perfusion** | Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from uninvolved bed in the same vessel or the opposite artery. |

**TIMI Thrombus Grading Scale** [*Gibson, 2001*]

| | |
|---|---|
| **Grade 0** | No angiographic evidence of thrombus |

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| | |
|---|---|
| **Grade 1** | Angiographic features suggestive of thrombus<br>• Decreased contrast density<br>• Haziness of contrast<br>• Irregular lesion contour<br>• A smooth convex meniscus at the site of a total occlusion<br>• Suggestive, but not firmly diagnostic of a thrombus |
| **Grade 2** | Definite thrombus present in multiple angiographic projections<br>• Marked irregular lesion contour with a significant filling defect – the thrombus' greatest dimension is < ½ vessel diameter |
| **Grade 3** | Definite thrombus appears in multiple angiographic views<br>• Greatest dimension from > ½ to < 2 vessel diameters |
| **Grade 4** | Definite large size thrombus present<br>• Greatest dimension ≥ 2 vessel diameters |
| **Grade 5** | Definite complete thrombotic occlusion of a vessel<br>• A convex margin that stains with contrast persisting for several cardiac cycles |

**Unanticipated Adverse Device Effect (UADE):** Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. [*21 CFR 812.3(s)*]

# 15.0 REFERENCES

Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, Fearon WF, Taggart D, Kappetein AP, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW; Academic Research Consortium. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Circulation. 2018 Jun 12;137(24):2635-2650.

# 16.0 REVISION HISTORY

| REV | Description of Change | Date |
|---|---|---|
| A | Initial release | 20 October 2020 |
| B | Updated primary efficacy and safety endpoints and added additional analysis for the primary endpoints and additional justification for the number of subjects. Added clarification that the Ringer perfusion balloon catheter is not intended for treatment of in-stent restenosis or expansion or delivery of a stent. | 24 February 2021 |
| C | Update to the date on the title page of the CRF. | 24 February 2021 |
| D | • Removed "Draft" from cover page.<br>• Added Kathleen Kearney, M.D. as the National PI to signature page. | 24 January 2022 |

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| REV | Description of Change | Date |
|---|---|---|
| | • Added ClinicalTrials.gov number to Regulatory Identification numbers.<br>• Updated site number from 3 to 5 to 4 to 7.<br>• Added sites enrollment cap of up to 15 subjects.<br>• Added REB – Research Ethics Board to Abbreviations List.<br>• Updated Section 8.3 to reflect current timeframe commitments.<br>• Added Research Ethics Board (REB) or REB to body of document wherever Institutional Review Board (IRB) or IRB is mentioned.<br>• Changed order of Inclusion criteria 6 and 7 to make consistent throughout document.<br>• Changed in Section 9.3 site enrollment from 30% to one-fourth.<br>• Changed in Section 11.1 definition of Transient Sinus Bradycardia from ≥50 BPM to ≥ 45 BPM.<br>• Added Section 16.0 REVISION HISTORY to document.<br>• General grammatical and spelling corrections. | |
| E | • Increase in site number and enrollment cap<br>• Change Study Sponsor Contact information | 21 March 2023 |

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