Statistical Analysis Plan

A Prospective, Multi-center, Non-Randomized Controlled Trial for A Novel Facilitated Antegrade Steering Technique in Revascularization of Coronary Chronic Total Occlusions in Chinese Population (FAST-CTO China)

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APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

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Revision History

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Version: AB	90702621 Rev/Ver AE	Section :4.1	Corrected the definition of analysis set	Sponsor corrections

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1 PROTOCOL SUMMARY

A Prospective, Multi-center, Non-Randomized Controlled Trial for A Novel Facilitated Antegrade Steering Technique in Revascularization of Coronary Chronic Total Occlusions In China Population(FAST-CTO China)	
Objective(s)	To assess the safety and efficacy of the Bridge Point CTO system in recanalization of CTO lesions in a multicenter study in Chinese population
Planned Indication(s) for Use	All subjects who are candidates for percutaneous coronary intervention (PCI), signed the informed consent form and had *chronic total coronary occlusion (CTO) lesion* will be evaluated for enrollment in this study.
Test Device	BridgePoint CTO System: • CrossBoss Catheter • Stingray LP Catheter • Stingray Guidewire and Extension Wire
Control Device	NA
Study Design	Prospective, multicenter, single-arm, observational study
Planned Number of Subjects	At least 100 subjects will be enrolled. Each site will be allowed to enroll up to a maximum of 25subjects.
Planned Number of Centers / Countries	Up to 10 investigational sites in China
Primary Safety Endpoint:	30-day MACE rate for CTO cases in which the BridgePoint Medical System was used. MACE is defined as the composite of cardiac death, Q-wave and non-Q-wave myocardial infarction(MI), and any ischemia-driven target lesion revascularization(TLR).
Primary Effectiveness Endpoint:	Technical Success: the ability of the BridgePoint Medical System to successfully facilitate placement of a guidewire beyond a CTO lesion in the true vessel lumen/within the collaterals
Secondary Endpoints	• Procedural success is a mean lesion diameter stenosis <50% in 2 near-orthogonal projections with TIMI 2-3 flow, as visually assessed by the physician, without the occurrence of in-hospital Q wave MI, TLR, or cardiac death. • Total procedure time • Total Fluoroscopy time and dose (mSv) • Total contrast dose • rate of MACE at 30 days, 6 months and 12 months • rate of stent thrombosis (ST) at 30 days, 6 months and 12 months • rate of cardiac tamponade through hospital discharge after the index procedure • rate of kidney failure caused by contrast through hospital discharge after

	the index procedure
Method of Assigning Patients to Treatment	NA
Follow-up Schedule	Subject follow up will occur via telephone contact or clinic visit at 30 days, 6and 12 months post index procedure, for all enrolled subjects.
Study Duration	About 2 years.
Required Medication Therapy	Based on the American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines and supported by the European Society of Cardiology (ESC) guidelines, dual antiplatelet therapy with aspirin and a clopidogrel is prescribed as follows to reduce the risk of thrombosis. **Aspirin**: • For subjects who have been taking aspirin for ≥ 72 hours at the time of the procedure, a loading dose is not required. But a 75-325 mg aspirin is recommended prior to the index procedure. • For subjects who have not been taking aspirin for ≥ 72 hours at the time of the procedure, a loading dose is recommended 24 hours prior to the index procedure, where the loading dose shall be decided by the investigator. • Subjects shall take aspirin indefinitely after the index procedure. **Thienopyridine** • For subjects who have been taking clopidogrel for ≥ 72 hours at the time of the index procedure, a loading dose is not required. • For subjects who have not been taking clopidogrel for ≥ 72 hours at the time of the index procedure, a loading dose is required. It is recommended that the loading dose be administered prior to the index procedure. However, in all cases, the loading dose is required to be administered not more than2 hours after the index procedure. The following loading doses are recommended: **Clopidogrel** • A peri-procedural loading dose of 600 mg is recommended. • Subjects must be treated with clopidogrel for at least 6 months following the index procedure. In subjects not at high risk of bleeding, clopidogrel treatment should continue for at least 12 months following the index procedure.

Key Inclusion Criteria	**Clinical Inclusion Criteria:** CI1. Subject must be ≥ 18 but < 80 years of age CI2. Subject (or legal guardian) understands the trial requirements and the treatment procedures and provides written informed consent before any trial-specific tests or procedures are performed CI3. Subject is eligible for percutaneous coronary intervention (PCI) CI4. Subject has symptomatic coronary artery disease or myocardial infraction (MI) with objective evidence of ischemia or silent ischemia CI5. Subject is an acceptable candidate for coronary artery bypass grafting (CABG) CI6. Subject is willing to comply with all protocol-required follow-up evaluation CI7. Subject has a left ventricular ejection fraction (LVEF) ≥45% as measured within 60 days prior to enrollment Angiographic Inclusion Criteria: AI1. A maximum of one de novo CTO lesion in a native coronary artery with thrombolysis in Myocardial Infarction (TIMI) flow grade 0 AI2. Non-acute CTO lesion with an estimated duration of at least 3 months by clinical history and/or comparison with previous angiogram or electrocardiogram(ECG) AI3. The CTO lesion must have an angiographic landing zone≥ 10 mm proximal to any major bifurcation without severe calcification. AI4. Lesion length < 40mm without excessive tortuosity and angulation(>45°)
Key Exclusion Criteria	**Clinical Exclusion Criteria:** CE1. Subject has clinical symptoms and/or ECG changes consistent with Acute MI(include STEMI and Non- STEMI) within 1 week CE2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmias, or ongoing intractable angina. CE3. Subject has received an organ transplant or is on a waiting list for an organ transplant CE4. Subject is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure CE5. Planned PCI (including staged procedures) or CABG after the index procedure CE6. Subject has a known allergy to contrast (that cannot be adequately pre-medicated)and/or protocol-required concomitant medications (e.g., aspirin or all thienopyridines) CE7. Subject has one of the following (as assessed prior to the index procedure): • Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of less than 12 months • Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.)

	• Planned procedure that may cause non-compliance with the protocol or confound data interpretation CE8. Subject is receiving chronic (≥72 hours) anticoagulation therapy (i.e., heparin, coumadin) CE9. Subject with out of range complete blood count (CBC) values that are determined by the study physician to be clinically significant. CE10. Subject has documented or suspected liver disease, including laboratory evidence of hepatitis CE11. Subject is on dialysis or has baseline serum creatinine level >2.0 mg/dL (177μmol/L) CE12. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions CE13. Subject has had a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months CE14. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding CE15. Subject has signs or symptoms of active heart failure (i.e., NYHA class IV) or LVEF < 45%at the time of the index procedure CE16. Subject is participating in another investigational drug or device clinical trial that has not reached its primary endpoint or intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure CE17. Subject had PCI within the previous 2 weeks CE18. Subject with known intention to procreate within 12 months after the index procedure (women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure) CE19. Subject is a woman who is pregnant or nursing (a pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential) **Angiographic Exclusion Criteria:** AE1. Target lesion is an aorto-ostial lesion or located in left main coronary artery, previous venous or arterial bypass grafts AE2. Target lesion involving a segment of previous stent AE3. Target vessel has excessive tortuosity and/or angulation proximal to the target lesion(>45°) AE4. Target lesion and/or the target vessel proximal to the target lesion is moderately to severely calcified by visual estimate AE5. Target lesion is located within 5 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCx) coronary artery by visual estimate AE6. Target lesion will be accessed via a saphenous vein graft or arterial graft

	AE7. Subject has unprotected left main coronary artery disease (>50% diameter stenosis) AE8. Thrombus, or possible thrombus, present in the target vessel (by visual estimate) AE9. Target vessel has a dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C
Statistical Methods	
Primary Statistical Hypothesis	There is no formal statistical hypothesis for this observational, single-arm study. In order to support the stated objectives, the sample size for this trial will be approximately 100 subjects. Descriptive statistics will be performed for key variables collected in the study. The detail will be documented in the statistical analysis plan.
Safety Parameters	All serious adverse events (SAE), adverse device effects (ADE), major adverse cardiac events (MACE) and stent thrombosis will be collected up to 12months follow-up intervals. A clinical events committee (CEC) will adjudicate for MACE and stent thrombosis through the 12-month follow-up.

2 INTRODUCTION

This statistical analysis plan addresses the planned analyses for A Novel Facilitated Antegrade Steering Technique in Revascularization of Coronary Chronic Total Occlusions in China Population (FAST-CTO China) based on protocol version AC dated 12 Nov 2019. Specified analyses may be used for scientific presentations and/or manuscripts, and regulatory submissions. It is a prospective, non-randomized, single-arm and multi-center post-marketing observational study, intended to collect intraoperative and postoperative clinical data of BridgePoint CTO Medical System in the revascularization of CTO lesions in China's real world settings. The Primary analysis will be based on 30 days post procedure. The study requires follow-up via telephone or clinical visit at the following time points: 30 days, 6 months and 12 months after the index procedure.

3 ENDPOINT ANALYSIS

All primary and secondary study endpoints will be assessed on the basis of intention to treat, i.e., analyzing all subjects who received BridgePoint CTO Medical System devices.

3.1 Primary Safety Endpoint

30-day MACE rate for CTO cases in which the BridgePoint Medical System was used.
MACE is defined as the composite of cardiac death, Q-wave and non-Q-wave myocardial infarction(MI), and any ischemia-driven target lesion revascularization(TLR).

The primary endpoint is summarized with counts and percentage and based on binomial proportion 95% CI will be presented for 30-day MACE and thus summarized based on the MACE definition by Cardiac death, Myocardial Infraction, Target Vessel Revascularization. The endpoint will be analyzed based on both ITT and PP population definitions.

3.1.1 Hypotheses

There is no specific hypothesis planned for this study.

3.1.2 Sample Size

The study planned to enroll 100 patients with CTO lesions and will use BridgePoint Medical CTO System for treatment.

3.1.3 Statistical Methods

For Primary safety endpoints, we calculate the 30-day Mace rate using the
Continuous variables (mean, standard deviation, observation number, minimum and maximum, 95% Confidence Interval).

3.2 Primary Effectiveness Endpoint

It is the Technical Success, the ability of the BridgePoint Medical System to successfully facilitate placement of a guidewire beyond a CTO lesion in the true vessel lumen/within the collaterals

The primary endpoint is summarized with counts and percentage and based on binomial proportion 95% CI will be presented for successfully facilitate placement of a guidewire and thus summarized. The endpoint will be analyzed based on both ITT and PP population definitions.

3.2.1 Hypotheses

There is no specific hypothesis planned for this study.

3.2.2 Sample Size

The study planned to enroll 100 patients with CTO lesions and will use BridgePoint Medical CTO System for treatment.

3.2.3 Statistical Methods

For Calculating the Primary Effectiveness, the discontinuous variables (percentage and number of events / number of samples) of baseline and clinical outcome variables will be summarized by descriptive statistics and for continuous variables (mean, standard deviation, observation number, minimum and maximum, 95% Confidence Interval) will be calculated.

3.3 Secondary Endpoint

The Secondary endpoints will be analyzed for all subjects at 30day, 6months, 12months and a one year follow up will be done for:

- Procedural success is a mean lesion diameter stenosis <50% in 2 near-orthogonal projections with TIMI 2-3 flow, as visually assessed by the physician, without the occurrence of in-hospital Q wave MI, TLR, or cardiac death.
- Total procedure time
- Total Fluoroscopy time and dose (mSv)
- Total contrast dose
- rate of MACE at 30 days, 6 months and 12 months
- rate of stent thrombosis (ST) at 30 days, 6 months and 12 months
- rate of cardiac tamponade through hospital discharge after the index procedure
- rate of kidney failure caused by contrast through hospital discharge after the index procedure

Secondary endpoint analysis are analyzed with both Intent to treat and per-protocol analysis and summarized with counts and percentage and based on binomial proportion 95% CI will be presented.

3.3.1 Hypotheses

There is no specific hypothesis planned for this study.

3.3.2 Sample Size

The study planned to enroll 100 patients with CTO lesions and will use BridgePoint Medical CTO System for treatment.

3.3.3 Statistical Methods

All the Secondary Endpoints will be calculated by collecting patient follow-up information during and post procedure, at hospital discharge or at 30 days, 6 months and 12 months post procedure as described in the clinical trial schedule, using descriptive statistics to summarize continuous variables such as procedure time and X-ray time (such as mean, standard deviation, observed value, minimum and maximum value) and discontinuous variables (frequency table or percentage).

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

All primary and Secondary endpoints will be analyzed both on an intent-to-treat (ITT) basis and on a per-protocol (PP) basis.

For intent-to-treat analyses, all patients who sign the IRB/IEC-approved study ICF and are enrolled in the study will be included in the analysis, regardless of whether or not a study device was implanted.

For per-protocol analyses, only patients who signed the IRB/IEC-approved study ICF and had used any component of BridgePoint Medical CTO System will be included in the analysis.

Effectiveness:
Primary effectiveness analysis will include enrolled subjects that meet all inclusion/exclusion criteria and use any component of BridgePoint Medical CTO System (CrossBoss catheter, Stingray LP catheter or Stingray guidewire).

Safety*:*
Safety analysis will include all enrolled subjects that use any component of BridgePoint Medical CTO System.

4.2 Control of Systematic Error/Bias

There is no randomization schema assigned in the study. The investigational devices/equipment shall be securely maintained, controlled, investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use and used only in this clinical study.

4.3 Number of Subjects per Investigative Site

There are 5-10 Investigational sites in china, At least 100 subjects will be enrolled. Each site will be allowed to enroll up to a maximum of 25subjects.

5 ADDITIONAL DATA ANALYSES

5.1 Baseline Comparability

Subject demographics, Physical assessment, Medical history, Angina assessment, LVEF, Cardiac medication, risk factors, and pre-procedure lesion characteristics will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables. No formal statistical testing will be done since this is a single-arm trial.

Lesion description both subject based and lesion based are also summarized with counts and percent for categorical data and descriptive statistics for continuous data. Pre-Procedural Lesion characteristics, and Post-Procedure Lesion characteristics are summarized and presented descriptively based on the data type.

5.2 Medications

Cardiac Medications are summarized with counts and percent for pre-procedure (<= 3 days & 14 days), Procedure, 30-days, 6-months and at 12-months. Antiplatelet medications are also summarized at pre-procedure(<=3 days), procedure, 30-days, 6-months and at 12-months with counts and percent.

5.3 Subject Disposition

Subject follow-up compliance summarized at 30-days, 6-months and 12-months' time with count and Subjects enrolled by site are summarized with counts.

5.4 Adverse Events

Non-serious AE's and SAE's will be summarized as the number of events and percentage of subject by MedDRA system organ class (SOC) and preferred term (PT). Frequency of site reported Serious adverse events and non-serious adverse events are presented. Also, procedure related serious and non-serious adverse events are summarized by SOC and PT. A listing based on deaths reported will also presented.

5.5 Protocol Deviations and Device Deficiencies

The definitions of Major Protocol deviations (PD) and Minor Protocol deviations (PD) are detailed below:

- Major PD is a protocol deviation that directly or potentially disrupts the study progress (i.e., the study design, study data and results can be compromised), OR a protocol deviation that compromises the rights, safety and welfare of study participants

- Minor PD is a protocol deviation that does not disrupt study progress (i.e., the study design, study data and results will not be compromised), AND does not compromise the rights, safety and welfare of study participants.

Major Protocol deviations and Minor Protocol deviations will be summarized for all Deviation categories and planned events by percentage of Subjects and by percentage of deviations.

5.6 Device Deficiencies

- Device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.
- All the Device deficiencies will be categorized at all the procedural time points and will be summarized

5.7 Interim Analyses

No formal Interim analysis are planned for this study.

5.8 Subgroup Analyses

No Subgroup analysis are planned for this study.

5.9 Justification of Pooling

This study will be conducted under a common protocol for each investigational site with the intention of pooling data for analysis. Every effort will be made to promote consistency in study execution at each investigational site.

5.10 Multivariable Analyses

No multivariate analysis is included for the primary, secondary or other endpoints.

5.11 Other Analyses

Clinical event rate will be expressed by percentage, and continuous variables will be expressed by number of samples, mean value, standard deviation, minimum and maximum value, where point estimation and 95% confidence limit will be provided.

5.12 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in a Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation and will documented in the clinical study report.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation. The validation level R1 chosen for all primary, secondary, safety and other additional endpoints. The validation program includes checking logs and generating compare reports in comparing with main programming datasets. Statistical analyses and validation will be performed by IQVIA team.

7 PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by IQVIA™ independently.

7.1 Statistical Software

All statistical analyses will be done using The SAS System Version 9.2 software or above (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.).

7.2 Format of Output

Results of analysis will be output programmatically to Microsoft Office® Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Methods for Handling Missing Data

No imputation method will be performed for the missing data handling.

Missed or late visits will be recorded as Protocol Deviations.

When calculating rates of all adverse events, both device and/or procedure related with missing event date (i.e. mm/dd/yyyy), the ideal is to work with safety and/or data management representatives to query sites for missing data. However missing and partial missing dates may be handled as using the worst case scenario as follows:

Partial Date	**Action Taken**
Entire adverse event onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.