A Prospective, Multi-center, Non-Randomized Controled Trial for A Novel Facilitated Antegrade Steering Technique in Revascularization of Coronary Chronic Total Occlusions In Chinese Population

(FAST-CTO China)

CLINICAL PROTOCOL

S2362

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Revision History

Revision Number	Protocol Date	Template number and version	Protocol Section Modifiied	Summary of Change	Justification for Modification
AB	10 Jun 2019	**92120219_Rev/Ver C**	Inclusion Criteria	1, 'Lesion length < 20mm' change to 'Lesion length < 40mm' 2, delete CTO must be "Verified" (aka "Refractory")	From Investigator's suggestion. (currently, most patients' lesion length> 20mm)
AB	10 Jun 2019	**92120219_Rev/Ver C**	Objective(s)	'To assess the safety and efficacy of the BridgePoint CTO system in recanalization of CTO lesions which are resistant to a conventional wire approach in a multicenter study in Chinese population' change to 'To assess the safety and efficacy of the BridgePoint CTO system in recanalization of CTO lesions in a multicenter study in Chinese population'	According to current guidelines/ consensus's suggestion.
AB	10 Jun 2019	**92120219_Rev/Ver C**	Primary Effectiveness Endpoint	Delete "in those cases that were otherwise refractory to treatment with a currently marketed guidewire" in the definition of Technical Success	According to the inclusion criteria and objective
AC	12 Nov 2019	**92120219_Rev/Ver C**	Device Sizes	Delete device sizes	Device Sizes information in the device registration certificate
AC	12 Nov 2019	**92120219_Rev/Ver C**	Test Device	"Stingray Catheter"change to "Stingray LP Catheter"	According to the device registration certificate

Revision History

Revision Number	Protocol Date	Template number and version	Protocol Section Modifiied	Summary of Change	Justification for Modification
AC	12 Nov 2019	**92120219_Rev/Ver C**	Contact information	Change PM from "Guangwei Yang" to "Chenchen Fan"	PM changed
AC	12 Nov 2019	**92120219_Rev/Ver C**	Contact information	Delete "Coordinating Co Principal Investigator"	There was no coordinating co principal investigator
AC	12 Nov 2019	**92120219_Rev/Ver C**	Risks Related to Study Device	Cardiac tamponade Recurrence of angina	According to the device Directions for Use
AC	12 Nov 2019	**92120219_Rev/Ver C**	Background	Change" These two products have been approved by CFDA and launch in China in 2014 ."to "These two products have been approved by CFDA and launch in China in 2014 and 2017."	Stingray LP Catheter have been approved by CFDA and launch in China in 2017

2. Protocol Synopsis

A Prospective, Multi-center, Non-Randomized Controled 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 BridgePoint 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 5 -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
Additional 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[ab], and supported by the European Society of Cardiology (ESC) guidelines[c], 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: o 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 arterywith thrombolysis in Myocardial Infarction (TIMI) flow grade 0 AI2. Non-acute CTO lesion with an estimated duration of at least 3 months by clincial 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	There is no formal statistical hypothesis for this observational,

Hypothesis	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.

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4. Background

At present, chronic total occlusion (CTO) is still the greatest challenge of percutaneous coronary revascularization to treat coronary atherosclerotic heart disease (CAD), and in fact, it is also the most common cause for a transfer treatment to the surgery of coronary artery bypass grafting (CABG) [1]. Treating CTO lesion through conventional percutaneous transluminal coronary angioplasty (PTCA) and/or stent implantation has been a widely accepted treatment method with good effects [2-5]. However, the success of PTCA or stent implantation depends on whether the conventional guidewire can cross CTO lesion or not. The conventional guidewire technology often fails to cross CTO lesion, so that the percutaneous method cannot be taken for treatment. The causes of failure to cross CTO lesion usually are: (a) insufficient force to cross the plaque that causes the occlusion; (b) mechanical guidewire trends to enter the subintimal pathway [6]; or (c) unable to operate the guidewire effectively towards the true vessel lumen to reenter the distal vessel of the CTO lesion. In the interventional procedure to treat CTO lesion, there are usually two ways to move the guidewire to cross CTO lesion: 1) in the true vessel lumen; or 2) along the vessel subintimal pathway. In fact, in CTO cases that lesion hinders the guidewire from crossing the true lumen, high-skilled interventional doctors develop a time consuming non-standard technology, attempting to use the special guidewire to cross the occlusion segment by subintimal pathway [7]. In almost 50% successful CTO lesion recanalization procedures carried out by these high-skilled interventional doctors, subintimal pathway and reentry into the true lumen are used [8].

BridgePoint Medical Inc acquired by Boston Scientific developed a new technology, intended to facilitate a safe and reliable crossing of CTO lesions, enabling the conventional guidewire to cross stenosed target lesion through true vessel lumen or subintimal pathway. BridgePoint Medical CTO System includes CrossBoss™ Catheter and Stingray™ system. CrossBoss Catheter is intended to help the guidewire cross stenosis lesion by getting through an intraluminal pathway crossing CTO lesion or building a subintimal pathway beyond CTO lesions. CrossBoss Cathetercombines the function of new recanalization guidewire and the supporting of probe catheter or recanalization catheter (please refer to section 2.1-2.3 for details).

In addition, BridgePoint Medical also developed a patent system to facilitate the reentry into the true lumen, which is applicable to the case that when CrossBoss Catheter has crossed CTO lesion but entered the vessel subintimal. This Stingray system includes Stingray Catheterand Stingray Guidewire and Extension Wire. Stingray catheter uses special technologies to facilitate the replacement of a guidewire in the true vessel lumen through the vessel subintimal pathway (please refer to section 5 for details). Stingray Guidewire and Extension Wire are used in conjunction with Stingray catheter, facilitating cardiologists to reenter a guidewire in the true vessel lumen through the vessel subintimal pathway (please refer to section 5 for details). These two products have been approved by CFDA and launch in China in 2014 and 2017.

BridgePoint Medical (BSCI) has conducted three clinical trials in the European Union and the United States, to assess the BridgePoint Medical CTO System.

4.1 First-in-man (FIM) Clinical Trial

Three sites in Santiago, Vina del Mar and Chile have made the first assessment for device feasibility and use of BridgePoint Medical CTO System in human subjects. For each subject, the objective is to use BridgePoint Medical device to cross CTO lesions, but the device selection is decided by physician preferences and/or lesion characteristics. 44 subjects have received the treatment, where 43 used CrossBoss catheter for treatment, 20 used Stingray catheter for treatment and 20 used Stingray guidewire for treatment. The procedural and 30 day post-procedural clinical follow-up results were evaluated. The following results include the clinical outcomes of all subjects that used BridgePoint Medical CTO System devices in treating refractory coronary artery CTO lesions.

4.1.1 Characteristics of the Subjects

The subjects that used BridgePoint Medical devices for treatment had an average age of 61.0 ± 10.4, where most subjects were male (77%). Most subjects suffered from mild or moderate hypertension (83%) and high cholesterol (63%). 46% subjects suffered from diabetes type I or type II and 32% subjects had a smoking history. 16% subjects had previous CABG procedure history and 15% subjects had family history of coronary heart disease.

4.1.2 Lesion Characteristic

CTO lesion is located in three main coronary arteries, where 42% in right coronary artery (RCA), 35% in left anterior descending (LAD) and 23% in left circumflex (LCX).

4.1.3 Technical and Procedure Success

Technical success is defined as the placement of a guidewire in the true vessel lumen outside the CTO distal end. Procedure success is defined as a successful recanalization of vessel (TIMI 3 flow). Technical success is realized in all subjects except for seven subjects, and then, revascularization is obtained successfully by drug eluting and/or placement of bare metal stent (37/44, 84%). Various methods are used in the procedure to achieve the success of the procedure. Table 4-1 summarizes the method to achieve technical success.

Table 4-2: Methods of Technical Success

Result	Number of subjects	Percentage of total subjects (%)
Use CrossBoss CTO catheter to enter the true lumen	24	55%
Use CrossBoss CTO Reentry System to reenter the true lumen	12	27%
Use a standard guidewire to cross and reenter	1	2%
Failed case	7	16%
Total	**44**	**100%**

Average procedure time is 99.5 ± 61.5 minutes. Average Fluoroscopy time is 32.1 ± 28.1 minutes, and average amount of radiation is 3.6 ± 2.3 Gray.

4.1.4 Safety

During the study, there was no acute adverse event. Retrospective follow-up was performed on 31 subjects 30 days after the procedure. In these 31 subjects, 3 (9.7%) experienced the adverse event within 30 days post procedure. Two subjects with an unsuccessful procedure had the angina again with slight myocardial enzymes elevation, and they received the CABG procedure subsequently. One subject had the angina again with slight (2x) troponin elevation after the procedure, but he did not receive a further treatment.

4.1.5 Conclusion

For BridgePoint Medical CTO devices, during the initial general clinical use, the devices represented a high success rate in entering CTO distal true lumen with acceptable short-term complication rates. Although subjects had no inclusion/exclusion criteria and surgeon lacked technical experiences of the system, the overall results still numerically showed a very low complication rates. Its clinical results showed a high learning curve and good performance in technically challenging cases.

4.2 European Union (EU) Clinical Trials

From July, 2008 to June, 2009, the second clinical trial was conducted in Germany. The trial originally planned to enroll 100 subjects, but it was terminated prematurely due to the incoming CE mark approval. Forty-two subjects were enrolled at four sites with CTO-PCI experience.

The primary objective of this trial is to test the efficacy and safety of CrossBoss, Stingray catheter and Stingray guidewire in facilitating the placement of a guidewire beyond a coronary artery CTO lesion distal end, while not increasing the incidence of major acute complications when compared to traditional guidewire / supporting catheter technologies. The secondary objective is to assess ergonomic and engineering performances of CrossBoss and Stingray devices from physician's preferences.

4.2.1 Clinical Trial Design

It is a prospective, non-randomized, and multi-center study on subjects with coronary artery CTO lesions, and the subjects 1) planned to receive interventional procedures by using standard guidewire and catheter facilities, or 2) planned to conduct a procedure to open or bypass CTO. Study results will be compared with safety and efficacy of traditional guidewire technology reported by literatures, and data will be collected in the process of using traditional guidewire to determine refractory CTO for comparison.

4.2.2 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the technical success. Technical success is defined as successful placement of a guidewire in the CTO distal true vessel lumen by using BridgePoint Medical System to cross the CTO lesion in those cases that were otherwise refractory to treatment with a currently marketed guidewire.

The published success rate that using a variety of mechanical guidewires, guiding and supporting catheters and/or CTO-special device combination to cross the CTO is between 39% to 100% [3-6,9-19]. If the data shows that in patients with CTO lesion that are uncrossable by using traditional guidewires, and the success rate is greater than 30% under 95% confidence level, the study is considered to be successful.

4.2.3 Secondary Efficacy Endpoint

Total procedure time and total Fluoroscopy time are the secondary efficacy endpoints of the study. One month (30 days) result will also be summarized in a table.

4.2.4 Safety Results

This study assessed relevant complications within 30 days after the procedure for BridgePoint Medical CTO System. Acute complications related to devices include:

- Perforation with hemopericardium or pericardial tamponade. AMI caused by CrossBoss and Stingray devices. AMI is defined as remarkable CPK elevation (> 3 times of the upper limit with positive MB results) and troponin level between 0.02 to 0.10 microg/L.
- MACE(including cardiogenic death, AMI related to lesions and emergent bypass procedure related to treatment segment) events.

4.2.5 Results

In all enrolled 42 subjects, the average age was 66 ± 9 years old, 85.7% were male, 31.0% suffered from diabetes. 16.7% subjects had CABG history and 45.2% suffered from MI previously. Table 4-2 below shows the overall statistics of enrolled subjects in the study.

Table 4-3: Statistics of Subject

Statistics	**results**
average age	66 ± 9 years (ranging from 48-83 years)
Gender (male)	36/42 (85.7%)
CABG history	7/42 (16.7%)

Statistics	**results**
MI history	19/42 (45.2%)
Hypertension (moderate and severe)	25/42 (59.9%)
Diabetes (all were type II)	13/42 (31.0%)
Hyperlipemia (moderate and severe)	12/40 (30.0%)
CAD family history	8/34 (23.5%)
Smoking history	11/41 (26.8%)
Angina	36/42 (85.7%)
CCS Angina classification (Class II or III)	34/36 (94.4%)
LVEF	56 ± 15%

4.2.5.1 Characteristics of vessel and lesion

The most commonly treated vessel was RCA (57.1%, 24/42), followed by LAD (21.4%, 9/42) and LCX (21.4%, 9/42). Nine subjects (21.4%) suffered from two vascular diseases and seven (16.7%) suffered from three vascular disease. The incidence of collateral branch bypass (circulation) is 41.5%. Additional characteristics of vessel and lesion can be found in Table 4-3 below.

Table 4-4: Characteristics of Lesion

Characteristics of lesion	**Result**
Average vessel diameter	2.9±0.4 (ranging from 2.0-3.5)
Average lesion length	36.0±30.1 (ranging from 3-150)
Tortuosity (moderate)	9/42 (21.4%)
Angulation (≥90˚)	10/42 (23.8%)
Calcification (moderate and severe)	9/42 (21.4%)
Collateral branch involvement (moderate and severe)	19/42 (45.2%)
Ipsilateral collateral branch Contralateral collateral branch	18/42 (42.9%) 24/42 (57.1%)
collateral branch bypass (circulation)	17/41 (41.5%)
Ostial lesion	2/42 (4.8%)
Proximal lesion	27/42 (64.3%)
Distal lesion	10/42 (23.8%)
Proximal to distal end	2/42 (4.8%)
Ostial to distal end	1/42 (2.4%)

4.2.5.2 Primary efficacy endpoint

In total 44 operations on 42 subjects, 28 subjects achieved the placement of the guidewire in CTO distal true lumen. Among them, one subject obtained the success after two procedures. The total success rate was 67% (28/42), slightly lower than the prespecified rate. Although the study only enrolled 42 subjects of the originally planned 100, the success rate was much higher than the historical benchmark result. Therefore, the study met the primary efficacy endpoint.

The study did not prespecify the rate of secondary procedure endpoint, however, its result was very prospective. Total procedure time and total fluoroscopy time incorporated in the literature were 146 minutes and 53 minutes respectively in average [19-23]. Total procedure time is defined as the time from inserting the first guiding catheter to withdrawing the last guiding catheter. The average procedure time of using BridgePoint Medical CTO System devices was 111±62 minutes (comparing to the literature average value, $p < 0.001$). The total X-ray radiation time of is defined

as the total time of exposure to the X-ray throughout the whole procedure. The Fluoroscopy time during the whole procedure was 41±22 minutes (compared with the average literature value, p = 0.008). The 30-day revascularization result matches its primary efficacy endpoint result of 28/42(67%).

4.2.5.3 Primary safety endpoint

This study had two complication events in total, both of which were non-Q-wave myocardial infarction (NQMI) related to collateral branch loss. The two complication events were both MACE, therefore, the rate of MACE is 4.8% (2/42). Although it is not statistically significant, this result is better than prespecified endpoint of 5/100 (p=ns); and it is lower than prespecified upper limit of MACE 12/100 (p=0.23). Therefore, the study met its primary safety endpoint. There was no perforation in this study (0.0%, 0/42), and its result is also better than prespecified endpoint of 6/100 (p=ns).

4.2.6 Conclusion

Although it only included 42 of planned 100 subjects, the study has overall beneficial results and achieves its safety and efficacy endpoint. Its primary efficacy endpoint (placing a guidewire in CTO distal true lumen) is significantly superior to the prespecified study endpoint ($p<0.005$). The primary safety endpoints, periprocedural AMI or perforation rate, are also within the prespecified ranges. The additional endpoints, total procedure time and total X-ray time, are also better than data in the existing literatures. High success rate and low complication rate observed in the study support to expand it to larger IDE trials.

4.3 FAST-CTO Clinical Trial

BridgePoint Medical CTO System was further assessed in FAST-CTO IDE clinical trial. On January 21st, 2009, FDA conditionally approved FAST-CTO IDE clinical trial (IDE #G080144). First subject was enrolled into the study on March 6th, 2009 and the last subject was enrolled on July 13th, 2010. A total of 147 subjects were enrolled at 16 sites. All subjects used one or more components of BridgePoint Medical System to treat at least one coronary artery chronic total occlusion (CTO) lesion. A summary of its clinical trial protocol and results are as following.

4.3.1 Study Objective

The primary objective of this trial is to test the efficacy and safety of CrossBoss, Stingray LP catheter and Stingray guidewire in facilitating the placement of a guidewire beyond a coronary artery CTO lesion distal end, while not increasing the incidence of major acute complications when compared to traditional techniques.

4.3.2 Study Design

The subjects enrolled in the FAST-CTO study had at least one refractory coronary artery CTO lesion. Data and Safety Monitoring Committee (DSMC) is responsible for auditing and adjudicating data during the whole study process. Similar to European Union study, primary safety endpoint is the incidence of MACE 30 days after the procedure. Primary efficacy endpoint is the technical success, and secondary efficacy endpoint includes total procedure time and total X-ray time.

4.3.3 Result

4.3.3.1 Demographic Characteristics of Subjects

Subject's demographic characteristics of FAST-CTO study are similar to those of subjects receiving CTO PCI in literatures, but its lesion length is longer than CTO lesion length reported in the existing literatures. The average CTO length of subjects is 32.3±20.8 mm. Demographic characteristics of subjects are shown in the table below. Most subjects were male (86%) and suffering from one or more accompanying diseases, such as diabetes, hyperlipaemia, hypertension,

family history of coronary artery disease and/or smoking history. Table 4-4 below summaries the demographic characteristics of subjects, which are classified according to total difficulty in crossing the lesion:

Table 4-5: Demographic Characteristics of Subjects Classified According to Refractoriness

Subject parameter	Total (n=147)	Failure history of previous operation (n=59)	Still difficult to cross for 10-15 minutes under perspective (n=50)	Guidewire enters the subintimal (n=38)	p-value
Age	63.3± 9.1	61.5± 9.3	64.7± 8.6	64.6± 9.1	0.02 [a]
Gender (male %)	86% (127/147)	85% (50/59)	86% (43/50)	89% (34/38)	0.83 [b]
Diabetes (type I or type II)	36% (53/147)	37% (22/59)	34% (17/50)	37% (14/38)	0.93 [b]
Hyperlipemia (moderate and severe)	62% (88/143)	58% (33/57)	80% (39/49)	43% (16/37)	0.002 [c]
Hypertension (moderate and severe)	52% (75/144)	43% (25/58)	61% (30/49)	54% (20/38)	0.18 [c]
CAD family history	37% (52/142)	49% (28/57)	31% (15/49)	25% (9/36)	0.04 [b]
Smoking history	19% (28/147)	22% (13/59)	10% (5/50)	26% (10/38)	0.10 [b]
Myocardial infarction history	39% (58/147)	34% (20/59)	44% (22/50)	42% (16/38)	0.55 [b]
Angina	86% (126/147)	83% (49/59)	90% (45/50)	84% (32/38)	0.57 [b]
CABG procedure history	22% (33/147)	17% (10/59)	28% (14/50)	24% (9/38)	0.39 [b]
History of previous attempts to cross CTO lesion	46% (67/147)	100% (59/59)	12% (6/50)	5% (2/38)	0.46 [d]

[a] Using Kruskal-Wallis test

[b] Using Freeman-Halton Exact test

[c] Using Freeman-Halton Exact test and comparing moderate / severe to none / slight

[d] Using Freeman-Halton Exact test and comparing the group with lesions that uncrossable after 10-15 minutes' attempt to the group that guidewire enters the subintimal

4.3.3.2 Characteristics of Target Vessel and CTO Lesion

Target vessels receiving treatments in this study included all three primary coronary arteries, where right coronary artery (RCA) accounted for the vast majority. Table 4-5 summaries target vessel and devices used in its treatment.

Table 4-6: Target Vessels And Devices Used

CTO vessel	Total (n=150)	Only CrossBoss cases (n=73)	True lumen reentry cases[a](n=77)	p-value[b]
Right coronary artery	71% (106/150)	75% (55/73)	66% (51/77)	0.24

Left anterior descending artery	19% (29/150)	14% (10/73)	25% (19/77)	
Left circumflex artery	10% (15/150)	11% (8/73)	9% (7/77)	

[a] Only including cases that used Stingray only and used all systems.

[b] Using Freeman-Halton Exact test

4.3.3.3 Primary Safety Endpoint

It was adjudicated by the Data and Safety Monitoring Committee (DSMC) that eight adverse events occurred on seven subjects met the definition of major adverse cardiac events (MACE), the primary safety endpoint. The incidence of 30-day MACE 4.8%, which is lower than the acceptable rate of 8.5% as described in clinical investigation plan (CIP), so that it can refuse a null hypothesis of 30-day MACE rate of 14% (p value is 0.0003). Therefore, FAST-CTO study met its primary safety endpoint. Table 4-6 summaries 30-day MACE and components of 30 days MACE.

Table 4-7: 30-Day MACE

Subject Events	Total (n=147)
MACE	4.8% (7/147)
Cardiac death	1.4% (2/147)
Q-wave MI	0.0% (0/147)
Non-Q-wave MI	4.1% (6/147)
Non-Q-wave MI [a]	4.2% (6/143)
Target lesion revascularization	0.0% (0/147)
Emergency CABG	0.0% (0/147)

[a] Excluding subjects that had no blood drawing or only one blood drawing in 6-8 hours.

4.3.3.4 Primary Efficacy Endpoint

Primary efficacy endpoint of FAST-CTO study is the technical success. Technical success is defined as the ability of the BridgePoint Medical System to successfully facilitate placement of a guidewire in the CTO distal true lumen. The total success rate is 76.7% (115/150) according to lesions and 76.9% (113/147) according to subjects. This result is better than 54%, the lower limit of success rate set in this study, and higher than 61%, the acceptable upper limit. If the true potential success rate is 54%, it is observed that among 150 CTO lesions, 115 or more lesions were successful and p value <0.0001 (provided that these CTO lesions were independent lesions). Similarly, if the true potential success rate is 54%, it is observed that among 147 subjects, 113 or more subjects were successful and p value <0.0001 (provided that the success rate is a constant). Table 4-7 summaries the technical success rate according to used devices. Although there was no independent classification to support it, the results in all used modes exceeded the primary efficacy endpoint threshold.

Table 4-8: Technical Success Classified by Used Devices

CTO endpoint	Total (n=150)	Only CrossBoss (n=73)	Reentry cases[a] (n=77)	p-value[b]
Technical success	77% (115/150)	77% (56/73)	77% (59/77)	1.00

[a] Only includes cases that used Stingray only and used all systems.

[b] Using Fisher's Exact test

4.3.3.5 Secondary Efficacy Endpoint

Total procedure time and total Fluoroscopy time are the secondary efficacy endpoints in FAST-CTO study. Total procedure time is calculated from starting to place the guiding catheter in the target vessel to withdrawing the last guiding catheter from the target vessel. If it is needed to determine the refractoriness of a lesion in the procedure, total time of procedure shall minus the procedure time that used to determine the refractoriness of a lesion. X-ray time is total time of X-ray during the procedure minus X-ray time needed for determination of the refractoriness of a lesion. The average total time of procedure is 105±54 minutes. The procedure time is remarkably less than historical data of 146 minutes (p value < 0.0001). The average total time of X-ray is 44±25 minutes, which is also remarkebly less than historical data of 53 minutes (p value < 0.0001).

As expected, failed procedures often needed a longer operation and X-ray time (Table 4-8) with a statistical significance.

Table 4-9: Procedure and X-ray Time in Successful and Failed Procedure

Measured values classified by procedure	Total (n=145)	Technical success (n=112)	Technical failure (n=33)	p-value[a]
Procedure time -Average value ± standard deviation - median (range)	 104.5±54.4 96 (17-332)	 98.7±50.9 90 (17-296)	 124.5±61.9 105 (46-332)	 0.02
X-ray time -Average value ± standard deviation - median (range)	 44.2±25.4 41 (5-163)	 41.4±24.2 38.5 (5-138)	 53.4±27.7 47 (10-163)	 0.01

[a] Using Wilcoxon test

4.3.3.6 Safety Data Summary Related to Perforation

Perforation rate in FAST-CTO study is similar to those observed in other CTO devices study (Table 4-9) [9-12, 24]. The total perforation rate in FAST-CTO study is 6.8% (10/147), where 5 (3.4%) cases are attributed to BridgePoint Medical devices by the surgeon. Compared to perforation rate (12.4%) summarized in the literature, in fact, the total perforation rate in FAST-CTO study is remarkbly lower than the summarized perforation rate in the literature (p value =0.02).

Table 4-10: Perforation Rate in Contemporary CTO Clinical Trials

Surgeon	Year	Device	Number of subjects (N)	Perforation (count)	Perforation (%)
Tiroch[23]	2008	Crosser	125	14*	11.2%
Baim[14]	2004	SafeCross	116	3	2.6%
Cannon[3]	2005	Crosser	45	0	0.0%
Hamburger[11]	1997	Prima	345	73	21.2%
Melzi[13]	2006	Crosser	28	1	3.6%
Oesterle[4]	1998	Prima	179	24	13.4%
Orlic[15]	2005	Frontrunner	50	9	18.0%
Corcos[10]	1998	CrossWire	56	2	3.6%
Morino[24]	2010	Guidewire	498	53**	10.6%
Summarized literature data			**1442**	**179**	**12.4%**
FAST-CTO			**147**	**10**	**6.8%**

*Including the following classifications defined in the paper: angiography result of guidewire exiting the true lumen (2.4%), myocardial blush of occluded location (2.4%), myocardial stain (4.8%) and adventitia spillage (angiography perforation, 1.6%).

** including perforation at CTO lesion location (36) and perforation in retrograde channel (17)

4.3.4 Conclusion

FAST-CTO clinical trial has successfully met its primary safety and efficacy endpoints, 30-day MACE and technical success. The study has also obtained positive results in procedure time, X-ray time and other secondary endpoints.

Summary of clinical trial

BridgePoint Medical CTO System has been assessed in many clinical trialsat different regions. The results of the above three trials showed its safety and performance, as well as consistently achieved safety and efficacy endpoints of the study. Using BridgePoint Medical CTO System can also reduce procedure and X-ray time.

5. Device Description

BridgePoint Medical CTO System (including CrossBoss Catheter, Stingray LP catheter and Stingray Guidewire and Extension Wire) is intended to facilitate the placement of a currently marketed guidewire in the lumen across coronary artery stenosis lesion (including chronic total occlusion) before PTCA or stent implantation.

Test Device :

CrossBoss Catheter

Stingray LP Catheter

Stingray Guidewire and Extension Wire

5.1 CrossBoss Catheter:

CrossBoss Catheter is a percutaneous catheter which is sterile and single-use with a diameter of 2.3F, designed to facilitate the cross of occlusion in coronary vessel. It is achieved by pushinhing the 1mm diameter distal tip of the device to the occluded location in the autologous vessel lumen and then rotating and pushing the catheter when necessary to facilitate the cross of stenosis lesion. This device is designed to deliver the guidewire across the diseased segment. After the placement of a conventional guidewire, PTCA catheter and/or stent can be used to provide treatment benefits. In addition to facilitating the cross of guidewire simply, no treatment effect or benefit is provided by BridgePoint Medical CrossBoss Catheter or itself.

The distal axle tube of CrossBoss Catheter provides a transition area between distal elasticity and turning expanded circular distal tips. The distal portion of CrossBoss Catheter has a hydrophilic coating, to enhance the lubricity. The torque meter is coaxially located above the proximal portion of CrossBoss Catheterr, to provide a comfortable user interface for device operations and provide a system based on ratchets at the same time, to prevent an excessive torque.

5.2 Stingray LP Catheter:

Stingray LP catheter is a 1.9F catheter which is sterile, single-use and overall exchange type, designed to further facilitate the placement of the guidewire across CTO lesion by achieving to reenter the true vessel lumen on the condition that conventional guidewire or CrossBoss Catheter has been pushed into the subintimal plane. It is achieved by using a distal expandable element, and when using a radiopaque contrast medium for expansion, it provides visibility and intra-arterial stability. The distal expandable element includes two small-caliber expandable balloons adjacent the guidewire cavity. When expanding, these small-caliber balloons and lumens are usually defined

as plane geometry, where the structural width is about 2.5 times of its height (2.5mm and 1mm respectively). In the expandable element, the distal portion of catheter includes two face-to-face side ports, connecting with the center guidewire cavity. These ports allow the operator to guide the guidewire to the catheter axis tube in the guidewire cavity at a certain angle. Expandable element and side port can achieve to locate the distal tip of guidewire properly and accurately, to allow the reentry of subintimal interior tissue without any injury to adventitia and outer vessel wall. The device provides a passageway for re-pushing the guidewire into CTO distal true vessel lumen in this way.

5.3 Stingray Guidewire and Extension Wire:

Stingray Guidewire and Extension Wire is a guidewire series which is sterile and single-use with a diameter of 0.014 inch, designed to facilitate the reentry of the guidewire into true vessel lumen during the use of the special reentry true lumen balloon dilatation catheter. In this device series, the distal portion of guidewire is designed to provide a variety of different distal elasticity. In addition, the distal portion also includes a platinum coil, to achieve the visibility. The distal tip of guidewire includes an angular geometric structure with transition to the circular tip. The short projecting portion (<0.014 inch) is protruded from the tip, helpful for the reentry into subintimal interior tissue smoothly without any injury to adventitia and outer vessel wall.

Similarly, like CrossBoss Catheter, PTCA, atherectomy and/or stent technology can be used to achieve treatment requirements once a guidewire is placed. Like CrossBoss Catheter, in addition to facilitating the cross of guidewire simply, no treatment effect or benefit is provided by Stingray LP catheter and Stingray Guidewire and Extension Wire.

5.4 Installation Instructions and the Use of Device

Installation instructions will be provided with each device, including information on device preparation and use. In addition, for cases using investigative devices, the sponsor personnel will also be present.

5.5 Necessary Training and Experience Required for Using Investigation Devices

BridgePoint Medical study personnel will give investigative device use, clinical investigation plan (CIP) and case report form (CRF) trainings to all sites. The device training will include device demonstration which is consistent with the direction for use (DFU), including device preparation and product operation. All site trainings will be recorded in the training form stored at the sites.

6. Study Objectives

To assess the safety and efficacy of the BridgePoint CTO system in recanalization of CTO lesions in a multicenter study in Chinese population.

7. Study Endpoints

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.

7.1 Primary Study 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
- 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, and any ischemia-driven target lesion revascularization. (for MI definition please refer to section 31.2)

7.2 Secondary Study Endpoint

- 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, defined as the time from inserting the first guiding catheter to withdrawing the last guiding catheter. If it is needed to determine the refractoriness of a lesion in the procedure, total procedure time shall minus the time used to determine the refractoriness of a lesion.
- Total fluoroscopy time (i.e., total fluoroscopy time recorded in the procedure minus fluoroscopy time needed in determining refractoriness of a lesion in the procedure) and total radiation dose (mSv) of X-ray
- 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 at hospital discharge after the index procedure
- Rate of kidney failure caused by contrast at hospital discharge after the index procedure

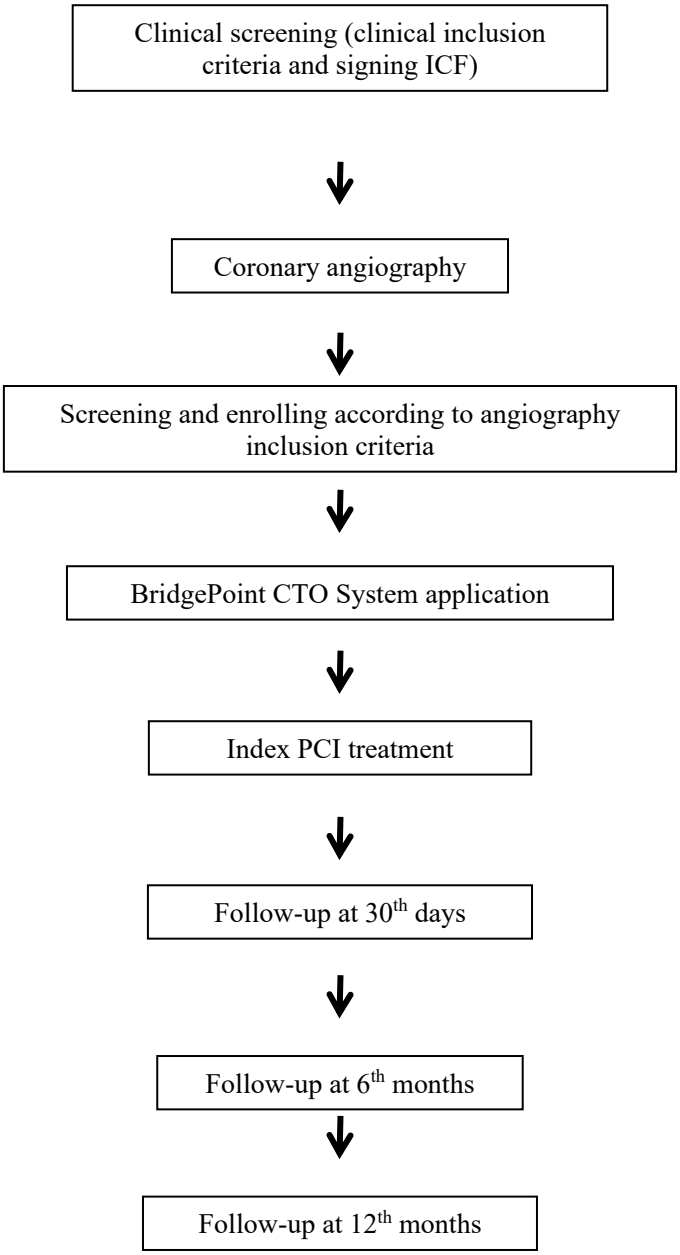
8. Study Design

FAST-CTO China clinical trial 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.

This trial planned to enroll 100 subjects at up to 10 sites in China. All subjects will be screened according to inclusion and exclusion criteria of the study protocol (see section 9).

100 subjects are expected to be enrolled within 12 months. 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. The study design flow is shown in Figure 8-1.

Figure 8-1: Study Design Flow Chart



9. Subject Enrollment

If a subject meets all clinical and angiography inclusion criteria (see section 9.2) and fails to meet any clinical and angiography exclusion criteria (see section 9.3), he/she can be enrolled into FAST-CTO China clinical trial.

9.1. 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 allprotocol-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 arterywith thrombolysis in Myocardial Infarction (TIMI) flow grade 0

AI2. Non-acute CTO lesion with an estimated duration of at least 3 months by clincial 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°)

9.2. 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 tothe target lesionis 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 lesionwill be accessed via a saphenous veingraft 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

10. Subject Accountability

10.1 Point of Enrollment

IF a subject signs an IRB/IEC approved informed consent form (ICF) and meets all inclusion criteria and fails to meet any exclusion criterion, it is considered that this subject is eligible to be enrolled into this study. The point of inserting any BridgePoint CTO device(s) into the body of the subject is the formal enrollment time point of this subject.

10.2 Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. Subjects may choose to withdraw from the study at any time, with or without reason and without prejudice to further treatment, although withdrawal is not encouraged. Withdrawn subjects will not undergo any additional follow-up, nor will they be replaced. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study. The investigator may discontinue a subject from participation in the trial if the investigator feels that the subject can no longer fully comply with the follow-up requirements of the trial or if any of the trial procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

10.3 Enrollment Controls

At least 100 subjects shall be enrolled at 5-10 China sites for this study and each site is allowed to enroll up to 25 subjects.

11. Study Methods

11.1 Data Collection

Data collection schedule of FAST-CTO China study is summarized in Table 11.1-1.

Table 11.1-1: Data Collection Schedule

	Pre-procedure ⩽14 days	Pre-procedure ⩽3days	Procedure	Post-procedure /prior to discharge	follow-up and visit		
					Telephone or hospital visit at 30 days (±7 days) [a]	Telephone or hospital visit at 6 months (±30 days) [a]	Telephone or hospital visit at 12 months (±30 days) [a]
Informed Consent Form[b], including date of signature		X					
Demographic data, including age and gender	X						
Physical assessment, including weight and height	X						
Medical history, including diabetes situation	X						
Angina assessment	X			X	X	X	X
LVEF[c]	X						
12 lead ECG		X		X			
Laboratory detection							
Serum creatinine and urea nitrogen	X						
complete blood count[d]	X						
Pregnancy test[e]	X						
Total CK/CK-MB		X[f]		X[g]			
Troponin[h]		X		X			
Cardiac medication	X	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]
Anticoagulant			X				
Antiplatelet drug		X	X	X	X	X	X
Recent previous PCI procedure information		X					

Table 11.1-1: Data Collection Schedule

	Pre-procedure ⩽14 days	Pre-procedure ⩽3days	Procedure	Post-procedure /prior to discharge	follow-up and visit		
					Telephone or hospital visit at 30 days (±7 days) [a]	Telephone or hospital visit at 6 months (±30 days) [a]	Telephone or hospital visit at 12 months (±30 days) [a]
Procedure, target lesion, pre-dilation, post-dilation (if applicable) and study stent information			X				
Angiography			X				
AE assessment[j]			X	X	X	X	X
ADE、SAE、SADE、UADE、USADE and device deficiency assessment[k]			X	X	X	X	X

a: All follow-up dates shall be calculated according to the index procedure. However, other protocol required follow-ups may be performed via telephone interview or an office visit within the applicable follow-up window.

b: If the study Informed Consent Form is modified during the course of the trial, study subjects will be re-consented, if necessary.

c: LVEF may be evaluated by angiography, echocardiogram, or radionuclide ventriculography within 60 days prior to enrollment.

d: Differential is only required for subjects who have abnormal leukocyte values.

e: A pregnancy test must be performed within7days prior to the index procedure in females of childbearing potential.

f: Preprocedure cardiac enzymes can be drawn from the sheath at the time of sheath insertion.

g: A minimum of 1 CK Total or CK-MB draw must be obtained within 1 day after the index procedure. If CK Total values are abnormal (>1× ULN), CK MB or troponin must be run.

h: If neither CK Total nor CK-MB is drawn, troponin must be drawn.

i: Collection is only required for subjects with any changes of cardiac medications.

j: All AEs will be monitored and reported to BSC from the time of enrollment through the 12-month follow-up for all subjects enrolled

k: ADEs, SAEs, SADEs, UADEs, USADEs, and device deficiencies will be monitored and reported to BSC from the time of enrollment through the 12-month follow-up for all subjects enrolled.

Abbreviations: AE= Adverse event; ADE= Adverse device effect; CBC= Complete blood count; CK= Creatine Kinase; CKMB= Creatine kinase isoenzyme; ECG= Electrocardiogram; PCI= Percutaneous coronary intervention; SADE= Severe adverse device effect; SAE= Severe adverse event; UADE=Unanticipated adverse device effect; USADE= Unanticipated severe adverse device effect

11.2 Screening of Study Subjects

This study will store a patient screening log, to record the information of subjects failing to meet eligibility criteria (including screening failure reasons) of FAST-CTO China study.

11.3 Informed Consent

Before any study specific tests or procedures are performed, subjects who meet the clinical eligibility criteria will be asked to sign the IRB/IEC-approved study ICF. Subjects must be given ample time to review the ICF and have questions answered before signing.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, catheterization may demonstrate that the subject is not a suitable candidate for the trial.

Refer to section 10.1 for definition of point of enrollment.

11.4 Up to 14 Days Prior to the Procedure

The following preprocedural data shall be collected within 14 days prior to the index procedure (unless otherwise stated):

- Confirmed to meet clinical eligibility criteria
- Demographic data, including age and gender
- Physical assessment, including weight and height
- Medical history (general condition, heart, nerve, kidney and peripheral medical history), including but not limited to the following:
    - Diabetes condition
    - Current angina condition
    - LVEF measured within 60 days prior to enrollment
- Laboratory detection
    - Serum creatinine and urea nitrogen
    - Complete blood count (CBC) and blood platelet
    - Women of child-bearing period are required to conduct the pregnancy test within 7 days prior to the procedure (according to local clinical routine practice, serum and/or urine)
- Current usage of cardiac medications

11.5 Concomitant Medication Required in This Study

For all subjects, a dual anti-platelet therapy (DAPT, i.e., aspirin and clopidogrel) is recommended according to current ACC/AHA/SCAI/ESC guide. Recommended DAPT dose regimen and treatment length are as follows:

Aspirin:

- For subjects who have been taking aspirin ≥ 72 hours at the time of the index procedure, a loading dose is not required but recommended. The loading dose shall be described at the investigator's decision .
- For subjects who have not been taking aspirin ≥ 72 hours at the time of the index procedure, a loading dose is recommended prior to the procedure (the loading dose is recommended 24

hours prior to the procedure but no later than 2 hours after the index procedure). The loading dose shall be described at the investigator's decision.

- All subjects shall take aspirin indefinitely after the index procedure.

$P2Y_{12}$ inhibitors

- 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 prior to the procedure (the loading dose is recommended to be prior to the procedure but no later than 2 hours after the index procedure). The loading dose of clopidogrel is recommended as 600mg.
- Subjects must be treated with clopidogrel for at least 6 months following the procedure. For subjects not at high risk of bleeding, clopidogrel treatment shall continue for at least 12 months following the procedure.

Index procedure / cath lab medication: a proper anticoagulant therapy shall be given in the procedure according to local standard treatment practice. If heparin is used, an activated clotting time (ACT) ＞ 250 seconds is recommended in the whole procedure.

11.6 Up to 3 Days Prior to the Index Procedure

The following preprocedural data of all subjects shall be collected within up to 3 days prior to the index procedure:

- Current antiplatelet medication
- Current cardiac medications; colletion is only required for subjects with any changes of cardiac medications
- 12 lead Electrocardiogram (ECG)
- Collection of the latest PCI procedure information, including treated vessel, location and procedure type
- Laboratory detection
  - Total CK or CK-MB (if the total CK is >1×ULN, CK-MB or troponin must be run)
  - Troponin (if CK / CK-MB cannot be run)

It is recommended that the same type of cardiac enzyme shall be collected prior to and after the procedure during the hospitalization (i.e., not converting from CK-MB to troponin, or vice versa).

Note: preprocedural cardiac enzymes can be drawn from the sheath at the time of sheath insertion.

11.7 Enrollment and Index Procedure

Use the standard catheter puncture technique to perform the procedure. The time of inserting the first guiding catheter is the start time of the procedure.

During the procedure, the following operation and assessment shall be completed:

- coronary artery angiography: all patients shall receive angiography assessment in the procedure according to standard clinical routine practice. Angiography data and films of enrolled subjects , as well as working records of technical personnel shall be submitted to Angiographic Core Laboratory for qualitative and quantitative analysis, including the confirmation of the guidewire's entery into the vessel subintimal. Angiography data and films of intervention on

non-target vessel in the index procedure do not need to be submitted to Angiographic Core Laboratory.

- Confirm the lesion meets the inclusion criteria of angiography and fails to meet any exclusion criterion of angiography.
-
- When BridgePoint CTO device facilitates a guidewire to cross the target lesion and the guidewire is confirmed to locate in the true vessel lumen or distal collateral branch vessel lumen of target lesion, all subjects shall receive PCI treatment on the target lesion according to local clinical practice, such as using balloon catheters to make pre-dilation, stent implantation, etc., to target lesion.

In this study, before the failure of BridgePoint CTO System device, other devices against CTO (such as Frontrunner, Crosser or SafeCross, etc.) shall not be used, but the intravascular ultrasound-guided true-lumen seeking and tracking (IVUS-TST) is allowed, i.e., the technique in which the guidewire can cross (or re-cross) the true lumen and move forward along the true lumen to the distal vessel under the guidance of IVUS and taking the occluded segment as the target.

11.8 End of Procedure / Prior to Hospital Discharge

The end time of procedure is defined as the time of removing the guiding catheter (after the final angiography). The following steps shall be completed after removing the catheter sheath according to local clinical routine practice:

- Record information of target lesion, guidewire and balloon catheter used, and information of pre-dilation, post-dilation (if applicable) and stent implantation and other information on corresponding eCRFs.
- Record procedure information on corresponding eCRFs, including start and end time of procedure, total fluoroscopy time of X-ray, total contrast dose used in the procedure, etc.
- Collect current cardiac medications: collection is only required for subjects with any changes of cardiac medications.
- Record anticoagulation and antiplatelet medications during the procedure.
- As described in section 24, complete recording and assessment of adverse events in the procedure and and collect source documents.
- 12 lead ECG within 1 day post procedure
- Laboratory detection
    - At least one CK Total or CK-MB draw must be obtained within 1 day after the index procedure. If the CK Total value is abnormal, CK-MB must be run.
    - If CK/CK-MB is not used, the troponin shall be run.

Note: it is recommended that the same type of cardiac enzymes shall be collected prior to and after the procedure during the hospitalization.

11.9 Follow-up

All subjects will receive assessments at the following points;

- 30-day follow-up (30 ± 7 days)
- 6-month follow-up (180 ± 30 days)

- 1-year follow-up (365 ± 30 days)

Follow-up may be performed via telephone interview or clinical visit. The following data will be collected at each follow-up visit:

- Collection and assessment of adverse events during the follow-ups, as well as collection of the source documents, as described in section 24
- Current angina condition assessment
- Current antiplatelet medications (aspirin and thiophene pyridines). Information on dose change, medication interruption and discontinuation must be recorded.
- Current cardiac medications: collection is only required for subjects with any changes of cardiac medications.

11.9.1 Loss to Follow-up

If a subject cannot return for follow up or cannot be contacted through telephone, at least 3 telephone contacts shall be made to obtain necessary information of the subject. All attempts shall be recorded in source documents. If a subject does not response to 3 telephone follow-ups, a letter must be sent to the subject in registered post subsequently. If a subject does not response to the letter, this subject shall be considered as a "loss to follow-up" of current study treatment or telephone contact. Investigators must attempt to contact the subject at each follow-up point and a registered mail shall be sent again if the subject cannot be contacted after 3 telephone contacts. Only after the subject cannot be contacted at the last follow-up, the subject shall be considered as a loss to follow-up and a study end form shall be filled.

11.10 Study End

A 12 months follow-up will be conducted to all subjects after the procedure. In order to assess the study endpoint, 12 months follow-up data of each subject must be collected.

11.11 Source Documents

Where copies of the original source document as well as printouts of original electronic source documents are retained, it is required that the copies be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document

12. Statistical Considerations

Study Endpoint

Primary Effectiveness Endpoint

Technical success is defined as 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

Safety Endpoint

30 days MACE is defined as cardiac death, Q-wave and non-Q-wave myocardial infarction (total CK is two times larger than normal upper limit and MB score is positive) and ischemia driven target lesion revascularization (TLR) .

Additional Study Endpoints

- Procedure 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, and the definition is the time from inserting the first guiding catheter to withdrawing the last guiding catheter minus the procedure time for determing the refractoriness of a lesion.
- Total time (i.e., total time of X-ray measured by site fluoroscopy system minus X-ray time for determining refractoriness of a lesion) and total radiation 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 before hospital discharge
- Rate of kidney failure caused by contrast before hospital discharge

11.2 Hypothesis and Sample Size

This study is an observational single-arm trial with no formal statistical hypothesis. The study planned to enroll 100 patients with CTO lesions, and will use BridgePoint Medical CTO System for treatment. The enrollment be completed at up to 10 sites.

11.3 General Statistical Methods

11.3.1 Analysis Set

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.

11.3.2 Data Analysis

Continuous variables (mean, standard deviation, observation number, minimum and maximum) and discontinuous variables (percentage and number of events / number of samples) of baseline and clinical outcome variables will be summarized by descriptive statistics.

This study will collect 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).

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.

12 Data Management

12.1 Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All

changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

12.2 Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for 10 years after study completion/termination, or follow the individual site guidance if the site required retention period is longer. BSC will retain these documents until the product/device is no longer in use according to local regulations.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12.3 Core Laboratory

FAST-CTO China study will use Angiographic Core Laboratory to analyze angiographic data. The result of Angiographic Core Laboratory will be input and uploaded to EDC system and provided to BSC only. For specific operations, refer to core laboratory operation manual.

Angiographic data of the index procedure and revascularization on target vessel at 1 year follow-up shall be submitted to Angiographic Core Laboratory for QCA analysis and assessment. Relevant data obtained outside the site shall also be sent to Core Laboratory for assessment.

13. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals from IRB/EC of the revised protocol must be obtained prior to implementation.

14. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC/REB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner

than 5 working days.

All protocol deviations (PDs) are classified to "major" and "minor"defined as below:

- A 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 safety and welfare of study participants.
- A 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 safety and welfare of study participants.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

15. Device / Equipment Inventory

This study is a post-marketing clinical study, and the sponsor will not provide investigational device / equipment.

16. Compliance

Statement of Compliance

This study will be conducted in accordance with ISO 14155:2011 (2nd Edition; 2011-02-01) Clinical Investigation of Medical Devices for Human Subjects- GCP, or the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and pertinent China's laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/IEC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/IEC or regulatory authority shall be followed, if appropriate

17. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency; and provide analysis report, which includes the causality assessed by both investigator and BSC and decision on study continuance, to IRB/EC per local and/or country requirements.
- Report all SAEs and device deficiencies that could have led to a SAE and potential/USADE or UADE to BSC by written documents, per the protocol requirements.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event; provide all required source documents related to a death event to BSC and the IEC per local requirements.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor and sponsor representatives to perform monitoring and auditing activities, and be accessible to theclinical research monitor or auditorand respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with

identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).

- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

18. Institutional Review Board/ Ethics Committee

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

19. Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including Contract Research Organization (CRO) will have access to these confidential records.Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and protocols for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

20. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and

follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy
- Boston Scientific personnel will not do the following.
- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

21. Insurance

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained. If any study related health injury occurs and a site is held responsible for its compensation, where required, BSC will assume the responsibility, except in the case that damages are incurred due to violation of the protocol, intentional or serious negligence at the site.

22. Monitoring

According to study monitoring plan, the monitoring shall be conducted during the whole study, to assess clinical study and approved protocol/amendment as well as compliance with relevant regulations. In addition, the monitor will check informed consent form from all enrolled subjects at the site, and preservation of study records, including data timeliness, completeness and accuracy and whether site has sufficient investigators and equipments to conduct this study safely and effectively. If protocol violations and compliance exceed the prespecified threshold, it will need to increase the site monitoring frequency and / or take corresponding corrective actions. Source documents shall include but are not limited to: informed consent forms (ICF), patient source medical record, angiographic results, laboratory results, SAEs reports and device inventory record forms. Data related to device deficiency, relationship between AE and study device, procedure and anticipatory assessment of ADE recorded on eCRF can also be considered as source data of this study. Source data verification (SDV) shall be performed on data reaching primary endpoints. SDV of this study can be reduced as appropriate after reaching primary endpoints.

Investigator / study site guarantees that Boston Scientific study personnel and its designated personnel and relevant regulatory authorities can check source documents directly (electronic source documents refer to the scanning documents signed and approved by clinician or hard copy source documents refer to hand-written medical records in clinical practice). If an source medical record cannot be obtained due to the reason that the subject was admitted to a non-study hospital and non-study doctor, copies of source documents shall be verified. As described in section 20, copies of source documents related to SAE (from site and non-study hospital, if applicable) need to be obtained and submitted to Boston Scientific Safety team.

This study may also be possible to be audited by Boston Scientific and its designated personnel, or

be inspected by supervision organizations. It shall be ensured that duiring the monitoring visit or inspection, investigators and other study personnel shall be present on site with plenty of time.

23. Potential Risks and Benefits

23.1 Risks Related to PCI / Stent Implantation

Potential AEs (in alphabetical order) which may be associated with the implantation of a coronary stent in a native coronary artery include those associated with percutaneous transluminal coronary angioplasty as well as additional risks related to the use of stents are listed below:

- Abrupt stent closure
- Acute MI
- Allergic reaction to anticoagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Arteriovenous fistula
- Bleeding
- Cardiac tamponade
- Cardiogenic shock/pulmonary edema
- Coronary aneurysm
- Death
- Dissection
- Emboli, distal (air, tissue, or thrombotic material or material from devices(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, which may require transfusion
- Hypotension/hypertension
- Infection, local or systemic
- Myocardial ischemia
- Pain at access site
- Perforation or rupture of coronary artery
- Pericardial effusion
- Femoral pseudoaneurysm,
- Renal insufficiency or failure
- Respiratory failure
- Restenosis of stented segment
- Stent deformation
- Stent embolization or migration
- Stent fracture
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

23.2 Risks Related to Study Device

Potential adverse events related to the use of BridgetPoint CTO System device include but are not limited to the following items;

- Acute myocardial infarction
- Vessel trauma requiring surgical repair or reintervention
- Massive hemorrhage or hematoma
- Arterial spasm
- Embolism
- Stroke
- Neurologic impairment
- Drug reactions, allergic reactions to contrast medium
- Infection
- Cardiac tamponade
- Recurrence of angina

23.3 Risks Related to Participating in Clinical Study

Except for the above risks of PCI and coronary artery stent implantation, long time use of dual antiplatelet treatment after the procedure may increase the risk of bleeding.

23.4 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

23.5 Anticipated Benefits

Anticipated benefits of this study is the ability to successfully facilitate the antegrade placement of a guidewire beyond a chronic complete occlusion lesion (CTO) in a PCI procedure, so that this kind of coronary artery lesions may receive interventional treatment and patient’s symptoms may improve.

23.6 Risk Benefit Ratio

BridgetPoint CTO System device is anticipated to achieve its intended treatment objectives. There are no unacceptable residual risks / intolerable risks, and all applicable risks have been stated in the product instruction for use. Anticipated risk and benefit assessment for BridgetPoint CTO System device states that its benefits exceed its risks under established conditions of use.

24. Safety Report

24.1 Definitions and Classifications

Table24-1: Safety Reporting Definitions

Term	Definition
Adverse Event(AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3 12*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related

Table24-1: Safety Reporting Definitions

Term	Definition
	to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3 /*	Adverse event related to the use of an investigational medical device NOTE 1: This includes any adverse event resulting from insufficiencies or inadequaciesin the instructions for use,the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that: Led to death, Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	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.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3* Note: only for clinical study outside of the United States, otherwise please delete this item	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155-* *Ref: MEDDEV 2.7/3*	A inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance.This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. **Note 1**: All device deficiencies that could have led to a SADE if a) suitable action had not been taken or b) if intervention had not been made or c) if circumstances had been less fortunate shall be reported as required by the local IRB/EC, national

Table24-1: Safety Reporting Definitions

Term	Definition
	regulations, or the protocol.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

Unless its severity or frequency increases during the study, basic diseases shall not be reported as AEs. Death shall not be reported as AEs and shall be reflected as a specific SAE outcome (AE definition is given in Table 24.1-1).

All AE of study subjects occurred after the enrollment, whether occurred during or after the procedure, shall be recorded in eCRF.

Known risks related to study device are given in section 23.

Device deficiency and other device problems shall not be reported as a AE. On the contrary, according to CRF completion guideline of this study, they shall be reported on corresponding eCRF (device deficiency form). If there are any AEs caused by device deficiency and other device problems, this AE shall be reported on corresponding eCRF (adverse event form).

In-patient hospitalization is defined as the subjects being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

24.2 Relationship to Study Device(s)

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 24-2.

Table 24-2: Criteria for Assessing Relationship of Study Device or Procedure to AE

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Classification	Description
Unlikely Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to;-the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Investigator must assess the relationship of the AE to the antiplatelet medication as related or unrelated. Criteria are defined in Table 24-3.

Table 24-3: Criteria for Assessing Relationship of Antiplatelet Medication to AE

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of a device/drug and is not determined to be potentially related to the antiplatelet medication.
Related	The adverse event is determined to be potentially related to the antiplatelet medication, and an alternative etiology is equally or less likely compared to the potential relationship to antiplatelet medication.

24.3 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 24-4.

Table 24-4: Investigator Reporting Requirements

Event Classification	**Communication Method**	Communication Timeline (pre-market studies)*	**Communication Timeline (post-market studies)****
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse	Complete AE eCRF page with all available new and updated information.	Special for China; Within 24 hours of first becoming aware of the event	Within 24 hours of first becoming aware of the event

Device Effect			
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	Special for China; Within 24 hours of first becoming aware of the event	Within 24 hours of first becoming aware of the event Reporting is required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	When source documents are available	When source documents are available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	Within 24 hours of first becoming aware of the event	Within 24 hours of first becoming aware of the event Reporting of ADEs is required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	When source documents are available	When source documents are available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete CRF Device Deficiency page with all available new and updated information.	Reporting is required within 24 hours of first becoming aware of the event through the end of the study.	Reporting is required within 24 hours of first becoming aware of the event through the end of the study.
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Timely report (such as , within 10 working days of first becoming aware of the event) • Reporting is required through the end of the study Special for China • no later than 10 working days of first becoming aware of the event • Reporting of AEs is required until the end of XXX follow-up Reporting of ADEs is	• Timely reporting (such as , within 30 of first becoming aware of the event) • Reporting is required through the end of the study

		required through the end of the study	

Abbreviations; AE=Adverse Event; CRF= Case Report Form; eCRF=Electronic Case Report Form; IDE= Investigational Device Exemption; UADE=Unanticipated Adverse Device Effect

25 Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in Device Management Plan. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF.

And, any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

Refer to Table 24-4 when reporting.

Reporting to Regulatory Authorities / IRBs / ECs / Investigators

BSC is responsible for reporting adverse event information and device deficienciesinformation to all participating Principal Investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

According to China local reporting requirements, Boston Scientific Corporation will report all SAEsand device deficienciesthat could lead to SAEs to the local regulatory authorities within 5 business days of BSC first becoming aware of the event, and notify all participating investigators/sitesand IRBs/ECs in a timely manner.

BSC shall notify all participating Chinese study centers if SAEs/SADEs occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

Boston Scientific Corporation, Investigator, or Site must notify the EC of UADEs, USADEs, SADEs, SAEs, Device Deficiencies and/or other CEC events as applicable according to local reporting requirements. A copy of the Investigator's reports and other relevant reports (if applicable) to the **IRB/IEC** must be provided to BSC in accordance with local requirements.

26 Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of

the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB/EC. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

Study personnel should explain to the subject that even if the subject agrees to participate in the trial and signs the ICF, catheterization may demonstrate that the subject is not a suitable candidate for the trial. A Screening Log will be maintained by the investigational site to document select information about candidates who fail to meet the trial eligibility criteria, including, but not limited

to, the reason for screen failure.

27 Committees

27.1 Safety Monitoring Process

To promote early detection of safety issues, the BSC Safety team and its delegated CRO Safety team will provide review, process, monitor and evaluation of the safety events defined in the study-specific safety plan. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information. The BSC Medical Safety group includes physicians with expertise in vascular intervention and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

27.2 Ethics Committee

Prior to the enrollment of subjects into this study and transportation of the study products, Boston Scientific must obtain a copy of the written approval (or allowance of performing this clinical study) to this protocol and informed consent form (ICF) that provided by EC and / or Institutional Review Board.

The investigator report and a copy of the EC approval letter shall be provided to the sponsor.

27.3 Clinical Events Committee

This study will use the Clinical Events Committee (CEC). CEC is an independent organization with relevant experiences, and CEC consists of cardiologists and cardiovascular interventional experts with relevant event adjudication experiences. Its responsibilities, qualifications, and CEC procedures will be listed in the CEC charter. CEC mainly reviews and adjudicates AE related to important clinical endpoints that reported by investigators. CEC committed member will review a safety event dossier, which may include source document copies of all TVR, MI (Q-wave or non-Q-wave) and death cases provided by site.

27.4 Executive Committee

An executive Committee composed of Boston Scientific clinical management personnel, study principle investigators and other experienced investigators. This committee will be responsible for the overall conduct of the study which will include protocol development, study progress, subject safety, data quality and integrity, and dissemination of study results through appropriate scientific sessions and publications. If applicable, Executive Committee may request participation of FAST-CTO China investigators on the Committee.

28 Suspension or Termination

28.1 Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

28.1.1 Criteria for Premature Termination of the Study

Reasons for premature termination of the study may include but are not limited to:

- Important new information that affects the continuation of the study (such as safety and product performance).
- Regulatory authorities does not agree to conduct this clinical study.

- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

28.2 Investigator Terminates the Study or Ethical Approval Withdrawal

Any investigator or EC of FAST-CTO China trial may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to BSC. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

28.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

28.4 Criteria for Suspending/ Termination of a Study Site

BSC reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled, if enrollment is significantly slower than expected, or if the center has multiple or severe protocol violations without justification and/or fails to follow remedial actions.

Adverse event assessment and reporting would continue for all subjects who received a study device. The Principal Investigator at the center must provide follow-up visits unless BSC notifies the investigational center otherwise.

29 Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee

at the onset of the project.

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31. Abbreviations and Definitions

31.1 Abbreviations

The abbreviations are shown in Table 31-1

Table 31-1: Abbreviations

Abbreviation/Acronym	Term
ACC	American College of Cardiology
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
ARC	Academic Research Consortium
BSC	BSC China
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CEC	Clinical Events Committee
CFDA	China Food and Drug Administration
CK	Creatine Kinase
CK-MB	Creatine Kinase-myoglobin band, a fraction of Creatine kinase
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
CVA	Cerebrovascular Accident
DES	Drug Eluting Stent
DFU	Directions for Use
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ESC	European Society of Cardiology
FHU	First Human Use
GCP	Good Clinical Practice
GI	Gastrointestinal
GUSTO	Global Use of Strategies for Opening Occluded Coronary Arteries
IABP	Intra Aortic Balloon Pump
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ISDN	Isosorbide Dinitrate
ISO	International Standards Organization
ITT	Intention to Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LAD	Left Anterior Descending Coronary Artery
LBBB	Left Bundle Branch Block

Table 31-1: Abbreviations

Abbreviation/Acronym	Term
LCX	Left Circumflex Coronary Artery
LMCA	Left Main Coronary Artery
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
MLD	Minimal Lumen Diameter
NHLBI	National Heart, lung, and Blood Institute
NTG	Nitroglycerin
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PLGA	Poly (DL-Lactide-co-Glycolic Acid)
POBA	Plain Old Balloon Angioplasty
QCA	Quantitative Coronary Angiography
RCA	Right Coronary Artery
RVD	Reference Vessel Diameter
SADE	Severe Adverse Device Effect
SAE	Severe Adverse Event
SCAI	Society for Cardiovascular Angiography and Interventions
STEMI	ST-segment Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in myocardial infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
ULN	Upper Limit of Normal
URL	Upper Reference Limit
US	the United States
WBC	White Blood Cell
WH	Workhouse

31.2 Definitions

Abrupt Closure

Abrupt closure is the occurrence of new severely reduced flow (TIMI grade 0 or 1) within the target vessel (including the side branch with a diameter of more than 1.5mm) that persists and requires bailout, including emergency surgery, or results in MI or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote “no reflow” due to microvascular flow limitation in which the epicardial artery is patent but has reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the assigned treatment reversed the closure.

Sub-abrupt closure is an abrupt closure that occurs after the target procedure is completed and the subject has left the catheterization laboratory and before hospital discharge.

Threatened abrupt closure is a grade B dissection and ≥50% diameter stenosis or any dissection of grade C or higher.

Adverse Device Effect (Reference: ISO 14155-2011, MEDDEV 2.7/3 12/2010)

Adverse event related to the use of an investigational medical device.

***Note*:** This definition includes AEs resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

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

Adverse Event (Reference: ISO 14155-2011, MEDDEV 2.7/3 12/2010)

Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. This includes events related to:

- The investigational medical device or comparator
- The procedures involved (study-required)

***Note*:** For users/other persons, this definition is restricted to events related to the investigational medical device

Adverse Event Relativity Terms

- Unrelated: The AE is determined to be due to a concurrent illness or effect of another device or drug and is not related to the investigational device.
- Related:
    - The AE is determined to be potentially related to the investigational device, and an alternative etiology is equally or less likely compared to a potential relationship to the investigational device.
    - There is a strong relationship to the investigational device or the event recurs on re-challenge, and another etiology is unlikely.
    - There is no other reasonable medical explanation for the event.

Annual Follow-ups

Annual follow-ups are those that occur annually through 5 years after the index procedure. The timing of annual follow-ups is calculated based on one calendar year equaling 365 days. The follow-up window is 30 days. Therefore, the 1-year, 2-year, 3-year, 4-year, and 5-year follow-ups should occur 365±30 days, 730±30 days, 1,095±30 days, 1,460±30 days, and 1,825±30 days after the index procedure, respectively.

Arrhythmia

An arrhythmia is any variation from the normal rhythm of the heart, including sinus arrhythmia, premature beats, heart block, atrial or ventricular fibrillation, atrial or ventricular flutter, and atrial or ventricular tachycardia.

Arteriovenous Fistula

An arteriovenous fistula is an abnormal passage or communication between an artery and a vein. It may result from injury or it may occur as a congenital abnormality.

Bailout

- Bailout typically refers to a peristent dissection but can also include a vessel complication at the ostium or along the course of the major coronary artery used to access the target lesion.
- The decision of whether to treat in a bailout situation is at the discretion of the interventionalist.
- If stenting is required in a bailout situation, the stent should be a study stent of the same type used to treat the target lesion.

Bifurcation Lesion

A bifurcation lesion is a lesion associated with the area where a branch vessel >2.0 mm in diameter by visual estimate originates.

Binary restenosis

Binary restenosis is a diameter stenosis >50% at the previously treated lesion site, including the original treated area and the adjacent proximal and distal QCA analysis segment.

Bleeding grading (Reference: GUSTO)

- Severe or life-threatening: massive intracranial bleeding or bleeding which will cause a hemodynamic functional injury and need an intervention treatment.
- Moderate: bleeding that needs a transfusion but will not cause any hemodynamic functional injury.
- Mild: bleeding that fails to meet the criteria of severe or moderate bleeding.

Braunwald Classification of Unstable Angina

Severity

- Class I: New onset, severe or accelerated angina. Subjects with angina of less than 2 months duration, severe or occurring 3 or more times per day, or angina that is distinctly more frequent and precipitated by distinctly less exertion; no pain at rest in the last 2 months.
- Class II: Angina at rest, subacute. Subjects with 1 or more episodes of angina at rest during the preceding month, but not within the preceding 48 hours.
- Class III: Angina at rest, acute. Subjects with 1 or more episodes of angina at rest within the preceding 48 hours.

Clinical Circumstances

- Class A: Secondary unstable angina. A clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia (e.g., anemia, fever, infection, hypotension, tachyarrhythmia, thyrotoxicosis, and hypoxemia secondary to respiratory failure).
- Class B: Primary unstable angina.
- Class C: Postinfarction unstable angina (within 2 weeks of documented MI).

Calcification

Readily apparent densities seen within the artery wall and site of lesion either as an X-ray absorbing mass or as an echogenic and shadow generating mass in IVUS imaging; these can be classified as little/none, moderate, or severe.

Canadian Cardiovascular Society Classification

- Class 1: Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
- Class 2: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or any

only during the first hours after awakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.
- Class 3: Marked limitations of ordinary physical activity. Walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.
- Class 4: Inability to carry on any physical activity without discomfort; angina syndrome

Pericardial Tamponade

Cardiac tamponade is an acute compression of the heart due to effusion of the fluid into the pericardium, or the collection of blood in the pericardium, from rupture of the heart or penetrating trauma.

Cardiogenic Shock

Cardiogenic shock is a clinical state with insufficient perfusion, represented as the systolic pressure <80 mmHg and/or the central filling pressure > 20 mmHg or the cardiac index <1.8 L/min/m^2, with evidences showing the insufficient perfusion of end-organ. If it needs to maintain the systolic pressure > 80 mmHg and the cardiac index > 1.8 L/min/m^2 by an intravenous injection of cardiac drugs and/or the use of intra aortic balloon pump (IABP), it is also considered as a shock. .

Cerebrovascular Accident

A CVA is a new focal neurological deficit of presumed vascular origin persisting more than 24 hours and with a neuro-imaging study that does not indicate a different etiology. The 24-hour criterion is excluded if the subject undergoes cerebrovascular surgery or dies during the first 24 hours. It includes subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. It does not include CVA events in cases of blood disorders such as leukemia, and it excludes subjects with a history of CVA secondary to trauma.

Creatine Kinase Myoglobin Band

Creatine kinase-myoglobin band (CK-MB) is an isoenzyme of creatine kinase (CK) with a distinct molecular structure specific as an indicator of myocardial cell injury. It is used to evaluate possible causes of chest pain, to detect and diagnose acute MI and re-infarction, and to monitor the severity of myocardial ischemia.

Clinical Events Committee

A CEC is an independent group of individuals with pertinent expertise that review and adjudicate important endpoints and relevant AEs reported by study investigators.

Clinical Events Committee Event

The CEC will adjudicate all reported cases of TVR, MI (Q-wave and non–Q-wave), and death (to ensure appropriate classification of death as cardiac or non-cardiac). A case adjudicated by the CEC is considered to be a CEC event.

Clinical Procedural Success (visual estimate)

Clinical 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.

Complication (angiographic or clinical)

A complication (angiographic or clinical) is an undesirable clinical event that results in death, injury, or invasive intervention. Complications may include, but are not limited to, perforation, occlusion, intimal flap, dissection, loss of side branch, distal embolization, non-fatal MI, elevated CK Total,

prolonged angina, hypotension, hematoma, arrhythmias, etc. Complications may or may not be related to the investigational device.

Congestive Heart Failure

Congestive heart failure is an inadequacy of the heart such that it fails to maintain adequate circulation of blood, so that congestion and edema develop in the tissues. Clinical syndrome is characterized by shortness of breath, non-pitting edema, enlargement of the liver, engorged neck veins, and pulmonary rales.

Coronary Aneurysm

A coronary aneurysm is a pathologic dilatation of a segment of a blood vessel involving all three layers of the vessel wall ≥1.5× the RVD.

Coronary Artery Spasm

Coronary artery spasm, or coronary vasospasm, is a spasm of a coronary artery, resulting in a decrease in lumen diameter. It may occur distal to the treatment site and is generally reversed with intracoronary administration of NTG or with adjunct balloon dilatation.

Death

Death is categorized as cardiac or non-cardiac.

Cardiac death is defined as death due to any of the following.

- Acute MI
- Cardiac perforation/pericardial tamponade
- Arrhythmia or conduction abnormality
- CVA through hospital discharge or CVA suspected of being related to the procedure
- Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery
- Any death in which a cardiac cause cannot be excluded

Non-cardiac death is defined as a death not due to cardiac causes as defined above.

De Novo Lesion

A coronary lesion not previously treated.

Device Deficiency (*Reference: ISO 14155-2011, MEDDEV 2.7/3 12/2010*)

A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

***Note**:* Device deficiencies include malfunctions, use errors, and inadequate labeling.

Dissection: NHLBI Classification

- Type A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material
- Type B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles
- Type C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material
- Type D: Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow

- Type E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen
- Type F: Filling defect accompanied by total coronary occlusion

Diabetes

Subjects will be categorized as having diabetes mellitus if medical treatment (oral or injection) is required for control of blood glucose levels.

Distal Embolization

Distal embolization is migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches.

Emergency Bypass Surgery

Emergency bypass surgery is CABG surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

Epicardial Vessel

Epicardial vessels include the LAD and its branches, the LCX and its branches, and the RCA and its branches.

Hypertension

Hypertension is persistently high arterial blood pressure. Various criteria for its threshold have been suggested, ranging from 140 mmHg systolic and 90 mmHg diastolic to as high as 220 mmHg systolic and 110 mmHg diastolic. Hypertension may have no known cause or be associated with other primary diseases.

Hypotension

Sustained hypotension is a systolic blood pressure less than 80 mmHg lasting more than 30 minutes or requiring intervention (e.g., pacing, IABP, intravenous vasopressors, to sustain systolic blood pressure). This excludes transient hypotension or vagal reactions, which are self-limited or readily reversible.

Index Procedure Start Time

Index procedure start time is defined as the time of guide catheter placement.

Index Procedure End Time

Index procedure end time is defined as the time the guide catheter is removed after the final angiography.

Intimal Flap

An intimal flap is an extension of the vessel wall into the arterial lumen.

Late Loss

Late loss is the postprocedure MLD minus the follow-up MLD as determined by QCA.

Left Main Coronary Artery Disease

Left main disease is a significant lesion in the left main coronary artery of at least 50% diameter stenosis. A protected left main artery means left main with a functioning graft, either venous or arterial, placed to any of the branches of the left main. This is usually the LAD or CX, but could also include one of the branches of those vessels. Having a stent in the left main coronary artery does not in itself constitute a protected left main.

Subject eligibility clarifications:

- Subjects with unprotected left main coronary artery disease may not be enrolled.
- Subjects with protected left main coronary artery disease are eligible for enrollment.

Left Ventricular Ejection Fraction

LVEF is an assessment of the amount of blood emptied from the left ventricle during systolic contraction, which is indicative of global ventricular function.

Lesion Characteristics (ACC/AHA classification)

- Type A lesions: Minimally complex, length <10 mm, concentric, readily accessible, non-angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.
- Type B lesions: Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guidewire, and some thrombus present.
- Type C lesions: Severely complex, diffuse (length ≥20 mm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

Refractory chronic total occlusion (CTO) lesion

the CTO lesion that cannot be crossed with conventional guidewires, which shall have any of the following situations:

- previous failed attempt to cross lesion within the past 12 months
- failed attempt to cross CTO with an antegrade guidewire for 10 - 15 minutes of fluoroscopy time
- attempt to cross CTO with an antegrade guidewire resulting in a subintimal wire position

Lesion Length

Lesion length is measured as distance from the proximal to the distal shoulder in the view that demonstrates the stenosis in its most elongated projection. Lesion length is classified as discrete (<10 mm), tubular (10-20 mm), or diffuse (>20 mm).

Lesion Location

Lesion location is the location of the lesion according to the specific coronary artery (i.e., left main, LAD, LCX, or RCA) or bypass graft, and is specified as proximal, mid, or distal. A standard map will be provided to be used for location descriptions.

Leukopenia

Leukopenia is a leukocyte count of $<3.0 \times 10^9$/liter for more than 3 days.

Malfunction

A malfunction is a failure of the device to meet performance specifications or otherwise perform as intended.

Myocardial Infarction

The definition of myocardial infarction in FAST-CTO China clinical trial:

Spontaneous myocardial infarction[25] (> 72 hours post procedure):

Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Graft (CABG) related Myocardial infarction [26] (≤ 72 hours post procedure)

1. CK-MB in patients with normal baseline concentration reaches any of the following criteria:
   - An increase in CK-MB peak to ≥10X URL during the first 48 hours following the procedure
   - An increase in CK-MB peak to ≥5X URL during the first 48 hours following the procedure, plus new pathological Q-wave in at least 2 contiguous leads, or new persistent LBBB

   Or meets any of the following criteria if CK-MB levels are unavailable and baseline troponin concentrations are normal:
   - An increase of troponin (I or T) to ≥70X URL during the first 48 hours following PCI
   - An increase of troponin (I or T) to ≥35X URL during the first 48 hours following PCI, and development of new pathological Q-wave in at least 2 contiguous leads or new persistent LBBB
2. In patient with elevated baseline CK-MB (or troponin) in whom the biomarker levels have shown the tendency to be stable or decrease, if the CK-MB (or troponin) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3. In patient with elevated baseline CK-MB (or troponin) in whom the biomarker levels have not shown to be stable or decrease, if the CK-MB (or troponin) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level, plus new ST-segment elevation or depression and clinical symptoms related to myocardial infarction, such as new or aggravated heart failure or persistent hypotension.

New York Heart Association classification

- Class I: Patients with no limitation of activities; they suffer no symptoms from ordinary activities
- Class II: Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion
- Class III: Patients with marked limitation of activity; they are comfortable at rest
- Class IV: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

Perforation

Perforations are classified as follows:

- Angiographic perforation: Perforation detected by clinical site or Angiographic Core Laboratory at any point during the procedure.

- Clinical perforation: Perforation requiring additional treatment, including efforts to seal the perforation or pericardial drainage, or resulting in significant pericardial effusion, abrupt closure, MI, or death.
- Pericardial hemorrhage/tamponade: Perforation causing tamponade.

Prolonged Angina Pectoris

Prolonged angina pectoris is angina lasting longer than 1 hour.

Pseudoaneurysm

A pseudoaneurysm is an encapsulated hematoma in communication with an artery. It is often difficult to distinguish from an expanding hematoma at the site of arterial puncture. It usually requires surgical repair.

Randomization

Randomization is the procedure by which subjects are assigned to a treatment group based on appropriate theories of probability including those involving random chance and conditional assignments.

Reference Diameter of Normal Arterial Segment

Reference diameter of the normal artery segment is an angiographic measurement of the artery proximal and/or distal to the lesion intended for angioplasty. This is also referred to as "reference vessel diameter" (RVD).

Repeated Intervention

Repeat intervention is a PCI or CABG performed after the end of the index procedure. The repeat intervention should be performed to improve blood flow.

Restenosis Lesion

A restenosed lesion is a previously treated lesion that again has a stenosis.

Restenosis

See Binary Restenosis.

Severe Adverse Device Effect (*Reference: ISO 14155-2011, MEDDEV 2.7/3 12/2010*)

Adverse device effect that has resulted in any of the consequences characteristic of a SAE.

Severe Adverse Event (*Reference*: *ISO 14155-2011, MEDDEV 2.7/3 12/2010*)

An adverse event that causes the following situations:

Adverse event that:

- Led to death
- Led to a serious deterioration in the health of the subject that either resulted in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization of existing hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
- Led to fetal distress fetal death or a congenital abnormality or birth defect

Stent Thrombosis (*Reference: the definition of Academic Research Consortium*) (44)

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guide catheter has been removed and the patient left the catheterization lab.

Timing:

- Acute stent thrombosis*: 0-24 hours after stent implantation
- Subacute stent thrombosis*: >24 hours to 30 days after stent implantation
- Late stent thrombosis: >30 days to 1 year after stent implantation
- Very late stent thrombosis: >1 year after stent implantation

* Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis is 0-30 days.

Stent thrombosis may be defined as:

- Confirmed/definite
- Probable
- Possible

Confirmed/Definite (is considered *either* angiographic confirmed or pathologic confirmed)

Angiographic confirmed stent thrombosis is considered to have occurred if:

- TIMI flow is:
  - TIMI flow grade 0 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of thrombus*
  - TIMI flow grade 1, 2 or 3 originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus*

AND at least one of the following criteria, up to 48 hours, has been fulfilled:

- New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes)
- New ischemic ECG changes suggestive of acute ischemia
- Typical rise and fall in cardiac biomarkers (>2× ULN of CK)

The incidental angiographic documentation of stent occlusion in the absence of clinical syndromes is not considered a confirmed stent thrombosis (silent thrombosis).

* Intracoronary thrombus

Non-occlusive thrombus: Spheric, ovoid or irregular non-calcified filling defect or lucency surrounded by contrast material (on 3 sides of within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive thrombus: A TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

Probable

Clinical definition of probable stent thrombosis is considered to have occurred in the following cases:

- Any unexplained death within the first 30 days
- Irrespective of the time after the index procedure and MI in the absence of any obvious cause which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis

Possible

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death beyond 30 days.

Stroke / Cerebrovascular Accident

An acute symptomatic episode of neurological dysfunction attributed to a vascular cause lasting more than 24 hours or lasting 24 hours or less with a brain imaging study or autopsy showing infarction.
Classification:

- Ischemic Stroke: An acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
- Hemorrhagic Stroke: An acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- Undetermined Stroke: A stroke with insufficient information to allow categorization as ischemic or hemorrhagic.

An event that lasts < 24 hours may be adjudicated as a stroke if the following treatments were used:

- Pharmacologic, i. e., thrombolytic drug administration, or
- Non-pharmacologic, i.e., neurointerventional procedure (*e.g.,* intracranial angioplasty)

Target Lesion

The target lesion is the lesion selected by the Investigator for treatment with a study device. The target lesion should meet the angiographic enrollment criteria. Only 1 target lesion can be treated during the index procedure as described in the enrollment criteria.

Target Lesion Failure (TLF)

Target lesion failure is any ischemia-driven revascularization of the target lesion, MI (Q-wave and non–Q-wave) related to the target vessel, or (cardiac) death. For the purposes of this protocol, if it cannot be determined with certainty whether the MI was related to the target vessel, it will be considered a TLF.

Target Lesion Revascularization (TLR)

Target lesion revascularization is any ischemia-driven repeat percutaneous intervention, to improve blood flow, of the successfully treated target lesion or bypass surgery of the target vessel with a graft distally to the successfully treated target lesion. A TLR will be considered as ischemia-driven if the target lesion diameter stenosis is ≥50% by QCA and there is presence of clinical or functional ischemia which cannot be explained by other coronary or graft lesions. Clinical or functional ischemia is any of the following:

- The subject has a positive functional study corresponding to the area served by the target lesion.
- The subject has ischemic ECG changes at rest in a distribution consistent with the target vessel.
- The subject has ischemic symptoms referable to the target lesion.

A TLR will be considered as ischemia-driven if the lesion diameter stenosis is ≥70% by QCA even in the absence of clinical or functional ischemia.

Target vessel

The target vessel is any coronary vessel (e.g., left main coronary artery, LAD, LCX, or RCA) containing a target lesion. Side branches of a target vessel such as the LAD are also considered part of the target vessel.

Target vessel failure (TVF)

Target vessel failure is any ischemia-driven revascularization of the target vessel, MI (Q-wave and non–Q-wave) related to the target vessel or (cardiac) death related to the target vessel. For the

purposes of this protocol, if it cannot be determined with certainty whether the MI was related to the target vessel, it will be considered a TVF.

Target Vessel Revascularization (TVR)

Target vessel revascularization is defined as a TLR (see definition above) or a TVR remote (see definition below).

Target Vessel Revascularization Remote

Target vessel revascularization remote is any ischemia-driven repeat percutaneous intervention, to improve blood flow, or bypass surgery of not previously existing lesions diameter stenosis ≥50% by QCA in the target vessel, excluding the target lesion. A TVR will be considered ischemia-driven if the target vessel diameter stenosis is ≥50% by QCA and any of the following are present:

- The subject has a positive functional study corresponding to the area served by the target vessel.
- The subject has ischemic ECG changes at rest in a distribution consistent with the target vessel.
- The subject has ischemic symptoms referable to the target vessel.

A TVR will also be considered as ischemia-driven if the lesion diameter stenosis is ≥70% even in the absence of clinical or functional ischemia.

Technical Success

Technical success is 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 in those cases that were otherwise refractory to treatment with a currently marketed guidewire.

Thrombus (angiography)

Thrombus (angiographic) is discrete, mobile intraluminal filling with defined borders with/without associated contrast straining, classified as either absent or present.

Thrombolysis in the Classification of Myocardial Infarction

- TIMI 0: No perfusion.
- TIMI 1: Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis of the duration of the cine run.
- TIMI 2: Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.
- TIMI 3: Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

Total Occlusion

A total occlusion is a lesion with no flow (i.e., TIMI flow 0).

Transient Ischemic Attack

A TIA is a focal ischemic neurological deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 hours of onset.

Unanticipated Adverse Device Effect (*Reference*: *21CFR Part 812*)

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 protocol 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.

Unanticipated Severe Adverse Device Effect (*Reference*: *ISO 14155-2011, MEDDEV 2.7/3 12/2110*)

A serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.