Terumo Study No.:	TIS2018-01
Version No.	1.4
Date	29JUL2020

TIS2018-01: **Cross-Seal™ IDE Trial:** Prospective, Multi-Center, Single Arm Study of the Cross-Seal™ Suture-Mediated Vascular Closure Device System

SPONSOR: Terumo Medical Corporation
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Clinical Protocol

Title:	**Cross-Seal IDE™ Trial:** Prospective, Multi-Center, Single Arm Study of the Cross-Seal™ Suture-Mediated Vascular Closure Device System
Study Number:	TIS2018-01
Investigational Device:	Cross-Seal™ Suture-Mediated Vascular Closure Device System (Cross-Seal™ System)
Study Type:	Prospective, multi-center, single arm
Version:	1.4
Version Date:	29JUL2020
Sponsor:	Terumo Medical Corporation

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A. Summary Of Changes

CIP Version	CIP Date	Description of change and rationale
1.0	**01 Jun 2018**	Initial Release
1.1	**14 Aug 2018**	• Eligibility criteria updated • Study Endpoints updated • Abbreviations and Definitions of Terms updated • Baseline visit assessments amended to include laboratory requirements and targeted groin exam • General and Procedural sections updated for additional requirements • Schedule of Events Table updated to reflect protocol changes • Concomitant Medication requirements updated regarding anticoagulants/anti-platelet use during index procedure • Potential Adverse Events updated • Minor clarification to text
1.2	**27Sep2018**	• Update to hypotension definition in procedural section
1.3	**30Oct2018**	• Update to statistical methods including performance goal for primary safety endpoint • Update of images and description for generation 2.2 knot tyer • Minor clarification to text
1.4	**29JUL2020**	• Change Sponsor address and study personnel update • For consistency across protocol and SAP - Clarified definition of “adjunctive treatment.” • Addition of unscheduled visit sand telephone assessment to assess safety of patients whose follow up visits were affected by COVID-19 • Update to statistical analysis sections to reflect imputation of data points and potential use of roll-in subjects if needed • Minor clarification to text

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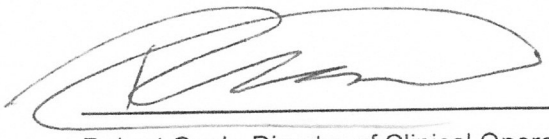
B. Protocol Approval Page

Study Title: **Cross-Seal IDE™ Trial:** Prospective, Multi-Center, Single Arm Study of the Cross-Seal™ Suture-Mediated Vascular Closure Device System

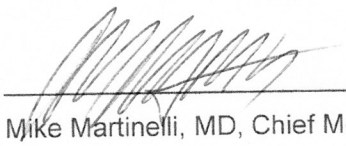
Study Number: TIS2018-01

PROTOCOL APPROVAL SIGNATURES AND DATES:



Robert Gash, Director of Clinical Operations.
Terumo Medical Corporation

14 AUG 2020
Date



Mike Martinelli, MD, Chief Medical Officer,
Sr. VP of Medical and Clinical Research
Terumo Medical Corporation

8/26/2020
Date

C. Study Roles and Responsibilities

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Core Laboratory: Syntactx

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Ethics Statement: The study will be completed in accordance with applicable regulations and standards to provide public assurance that

the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

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D. Investigator Approval and Agreement

PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt, review and understanding of the protocol entitled, "**Cross-Seal™ IDE Trial:** Prospective, Multi-Center, Single Arm Study of the Cross-Seal™ Suture-Mediated Vascular Closure Device System " and any attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the signed Clinical Trial Research Agreement (CTRA), protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations.

_____ _____

Investigator Signature Date (DD/MMM/YYYY)

_____

Investigator Name (please print)

_____

Investigator Institution (please print)

E. Study Summary

Study Design

This is a prospective, multi-center, single arm, clinical study to investigate the safety and efficacy of the Cross-Seal™ System.

Investigational Device and Indications for Use

The Cross-Seal™ System is indicated for the percutaneous delivery of sutures for closing the common femoral artery access site of subjects who have undergone interventional catheterization procedures using 8Fr to 18Fr sheaths.

Target Subject Population

The target population is comprised of subjects scheduled for elective percutaneous intervention with introducer sheath sizes of 8-18Fr and planned percutaneous arteriotomy closure. Applicable procedures include Transcatheter Aortic Valve Replacement (TAVR), Endovascular Aneurysm Repair (EVAR). Thoracic Endovascular Aneurysm Repair (TEVAR) and Balloon Aortic Valvuloplasty (BAV).

Study Center(s) and Number of Subjects Planned

A minimum of 3 sites and up to 25 sites in the US are expected to participate in the study with approximately 100 pivotal subjects enrolled. No more than 15% of the pivotal subjects may be enrolled at a single investigational site.

The first 1-2 subjects enrolled by each investigator will be considered roll-in subjects to allow for physician experience with the investigational device. A maximum of 3 study investigators and 6 roll-in subjects will be permitted at each investigational site.

In total, up to 250 subjects will receive the investigational device as part of the clinical study.

Study Duration

Study enrollment is expected to occur over a 10 to 12-month period. Imaging and follow-up procedures will continue through 30 days post-procedure. Subjects with an abnormal Duplex Ultrasound (DUS) at 30 days will have a repeat DUS at 60 days post-procedure

(all DUS will be analyzed by an independent core laboratory). The total study duration is expected to be approximately 24 months.

Note: Due to the COVID-19 pandemic, some patient follow-up visits have been delayed greater than 6 months or completely missed; therefore, making data collection extremely difficult (e.g., missed DUS assessments) to support some of the secondary endpoints. To evaluate safety, we have added an unscheduled visit and telephone assessment (if needed) to be conducted as soon as possible based on physician and hospital regulatory discretion.

Study Objective

The study objective is to demonstrate the safety and efficacy of the investigational device to achieve hemostasis of common femoral artery access site in subjects undergoing percutaneous endovascular procedures utilizing 8-18Fr introducer sheath.

Study Hypothesis

Safety:

The freedom from major complications at the target limb access site within 30 days post-procedure will be greater than the specified Performance Goal (PG).

Efficacy:

Following use of the investigational device, the mean Time-to-Hemostasis (TTH) will be less than the specified PG.

Endpoints

The following study endpoints will be evaluated:

Primary Safety Endpoint:

- Freedom from major complications of the target limb access site within 30 days post-procedure which includes the following:

Major Complications:

- Vascular injury attributable to the investigational device that requires surgical repair, stent-graft, or balloon angioplasty

- Access site-related bleeding attributable to the investigational device that requires transfusion
- Any new access site-related ipsilateral lower extremity ischemia attributable to the investigational device and documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram
- Surgery for access site-related nerve injury attributable to the investigational device
- Permanent (lasting > 30 days) access site-related nerve injury attributable to the investigational device
- Access site infection requiring intravenous antibiotics and/or extended hospitalization

Primary Efficacy Endpoint:

- The mean TTH in the Common Femoral Artery (CFA) of the target limb access site with use of the investigational device.

  TTH will be evaluated from time of procedural sheath removal to first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing at access site) in the target limb for subjects not requiring adjunctive intervention.

  If a sheathless system is used during the procedure, TTH will be calculated from final introducer sheath removal to first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing at access site) in the target limb for subjects not requiring adjunctive intervention.

  Adjunctive Intervention is defined as any use of surgical or endovascular intervention OR firm/occlusive manual pressure needed to achieve access site hemostasis (light/non-occlusive pressure to control cutaneous or subcutaneous oozing at the access site is excluded).

Secondary Safety Endpoints:

- The freedom from minor complications at the target limb access site within 30 days post-procedure including the following:

Minor Complications:

- Non-treated pseudoaneurysm attributable to the investigational device and documented by DUS
- Pseudoaneurysm attributable to the investigational device and treated with ultrasound-guided compression, ultrasound-guided thrombin injection. or ultrasound-guided fibrin adhesive injection
- Non-treated or treated arteriovenous (AV) fistula attributable to the investigational device and documented by DUS
- Access site hematoma greater than or equal to 10 cm in diameter, attributable to the investigational device, and confirmed by DUS
- Late (following hospital discharge) access site-related bleeding in target limb
- Lower extremity arterial emboli attributable to the investigational device
- Vein thrombosis attributable to the investigational device
- Transient access site-related nerve injury attributable to the investigational device
- Access site wound dehiscence
- Access site infection treated with intramuscular or oral antibiotics

- Device Related Complications (DRCs) and procedural complications within 30 days post-procedure
- Evaluation of all Adverse Events (AEs) from time of investigational device use within 30 days post-procedure, and through 60 days post-procedure for subject's requiring a repeat DUS, including major and minor complications

Secondary Efficacy Endpoints:

- Technical Success: defined as achievement of hemostasis with the investigational device without the need for any access-site-related adjunctive surgical or endovascular intervention (target limb only).
- Access site closure success: defined as technical success and freedom from major complications within 48 hours of the index procedure or hospital discharge, whichever occurs first (target limb only).
- Treatment Success: defined as technical success and freedom from major complications through 30 days follow-up.

- Subjects requiring adjunctive surgical or endovascular intervention to achieve hemostasis of the access site (target limb only) including type of adjunctive intervention.
- Subjects receiving adjunctive manual compression following use of the investigational device to achieve hemostasis of the access site (target limb only).
    - Type of compression applied (light or firm, where light compression is defined as non-occlusive (i.e., "patent hemostasis") allowing distal blood flow, and firm compression defined as occlusive prohibiting distal blood flow.
- Time-to-Ambulation: defined as elapsed time from final procedural sheath removal to time when the subject stands and walks at least 20 feet without re-bleeding.
- Time-to-Discharge (i.e., time of actual discharge defined as the elapsed time between final procedural sheath removal and when the subject is actually discharged from the hospital)
- Occurrence of device failure as defined in Section 13.0

Exploratory Endpoints:

- Time-to-Device-Deployment defined as time of guidewire removal during device insertion to time of guidewire reinsertion during device removal, and overall procedure time defined as time of first skin nick/incision to achievement of hemostasis in the access site (target limb only)
- Time-to-Dischargeability (i.e., discharge eligibility defined as the elapsed time between final procedural sheath removal and time when the subject is medically able to be discharged based solely on the assessment of the access site as determined by the investigator.

Statistical Methods

Sample Size Determination

The sample size calculations were performed using PASS 2020 Version 20.0.2[i]. The appendix included the output from the software. The sample size for the study is based on power considerations for the primary effectiveness endpoint. As will be described below, this sample size should also provide adequate power for the primary safety endpoint.

Primary Efficacy Endpoint

The primary effectiveness hypothesis will be tested by comparing the primary effectiveness endpoint, mean time-to-hemostasis (TTH), against a performance goal (PG) of 15 minutes.

The comparison to the performance goal will be based on the following statistical hypothesis test:

$$H_O: \mu_{TTH} \geq 15$$

$$H_A: \mu_{TTH} < 15$$

where $\mu_{TTH}$is the mean time-to-hemostasis in minutes.

The test will be based on whether the upper one-sided 97.5% confidence limit (based on a t-distribution)[ii] is less than 15. Assuming similar performance to Perclose ProGlide®, with a mean time-to-hemostasis of 9.8 minutes and a standard deviation of 17 minutes the sample sizes for power levels from 80 to 90%

a Table 1: Primary Efficacy Endpoint Sample Sizes for Various levels of Power

Power	Sample Size	Maximum Observed Time (minutes) and still reject H_0
80.0%	86	10.8
81.4%	89	10.9
82.3%	91	10.9
83.1%	93	10.9
84.3%	96	11.0
85.0%	98	11.1

Successful rejection of the null hypothesis will mean that the PG has been met.

Primary Safety Endpoint

The primary safety hypothesis will be tested by comparing the primary safety endpoint, freedom from major complications of the target limb access site within 30 days post-procedure, against a performance goal.

The comparison to the performance goal will be based on the following statistical hypothesis test:

$$H_0: p \leq 85.2\%$$

$$H_A: p > 85.2\%$$

where *p* is the safety endpoint rate for the test device.

Assuming similar performance as ProGlide (an event-free rate of 94%), one-sided alpha = 0.05, the sample sizes for various levels of power are:

Table 2: Primary Safety Endpoint Sample Sizes for Various levels of Power

Power	Sample Size	Minimum # of Event Free Patients needed to reject the H_0
81.3%	78	72
85.6%	86	79
88.3%	95	87

F. List of Abbreviations and Definition of Terms

AE:	Adverse Event
ACT:	Activated Clotting Time
AV:	Arteriovenous
BAV:	Balloon Valvuloplasty
BMI:	Body Mass Index
CE:	Conformité Européene
CEC:	Clinical Events Committee
CFA:	Common Femoral Artery
CFR:	Code of Federal Regulations
CIP:	Clinical Investigational Plan
CRO:	Clinical Research Organization
CTRA:	Clinical Trial Research Agreement
CVD:	Cardiovascular Disease
DRC:	Device Related Complication
DSMB:	Data Safety Monitoring Board
DUS:	Duplex Ultrasound
eCRF:	Electronic Case Report Form
EVAR:	Endovascular Aneurysm Repair
FIH:	First-in-Human
GMP:	Good Manufacturing Practice
HIPAA:	Health Care Portability and Accountability Act
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
IFU:	Instructions for Use
IRB:	Institutional Review Board
LVEF	Left Ventricular Ejection Fraction
MI:	Myocardial Infarction
PC:	Percutaneous
PG:	Performance Goal
SAE:	Serious Adverse Event
SC :	Surgical Cut-down
SDV :	Source Document Verification
STEMI :	ST Elevated Myocardial Infarction
TAVR:	Transcatheter Aortic Valve Replacement
TEVAR:	Thoracic Endovascular Aneurysm Repair
TTH:	Time to Hemostasis
UADE:	Unanticipated Adverse Device Effect
VCD:	Vascular Closure Device

1 Background

Cardiovascular disease (CVD) is the number one cause of death in the United States and worldwide. In 2012 an estimated 17.5 million people worldwide died from CVD and by 2030 more than 23 million people will die annually.[1] The older population is growing faster than the total population in almost all regions of the world and the difference in growth rates is increasing. According to the US Census Bureau there will be 71 million people above the age of 65 years, and 19.5 million above the age of 80 in 2030.[2] People age 85 and over are now the fastest growing portion of many national populations.[3] As the aging population continues to rise, there is a corresponding increase in the number of percutaneous radiologic and endovascular procedures to address CVD. As a result, there are continued efforts to improve patient outcomes while reducing procedural related complications and health care utilization. As procedure complexity rapidly increases, often involving multiple access points needed for advanced disease treatment, efforts to improve outcomes and reduce complications are increasingly focused on improvements of vascular access closure.

One area of percutaneous vascular interventions that has received considerable focus in the past decade relates to technologies to achieve rapid and effective control of femoral arterial access. Traditionally, cardiac and peripheral interventions have involved 5–8Fr sheaths with hemostasis achieved with manual compression at the vascular access site.[4] Manual compression is associated with extended bed rest/hospital stay and patient discomfort. Arteriotomy closure devices were introduced in 1995 as adjuncts or alternatives to manual compression in an attempt to reduce vascular complications, reduce time to hemostasis and ambulation and improve patient comfort.[5] Currently, a number of vascular closure devices (VCD) exist for closure of small femoral arterial access sites. These devices are categorized by mechanism that include collagen plug devices such as Angio-Seal™ (Terumo Corporation, Tokyo, JP); clip-based closure : StarClose SE® (Abbott Vascular, Santa Clara, CA, USA); sealing agents: Mynx® (AccessClosure, Mountain View, CA, USA); and sutures for placement around the femoral artery: Prostar XL® Percutaneous Vascular Surgical Device and Perclose ProGlide® Suture-Mediated Closure System (Abbott Vascular, CA, USA).[6] These closure devices have primary been developed for peripheral interventions.

1.1 Need For Large Arteriotomy VCD

An increasing number of interventional procedures require large-sheath technology (> 12 Fr), including abdominal aortic aneurysm repair, thoracic aortic aneurysm repair, balloon valvuloplasty, percutaneous aortic valve replacement, and a variety of percutaneous ventricular-assist devices. These procedures create challenges for hemostasis and minimization of vascular complications. The ability to achieve access and closure without surgical cut-down has become an important part of the vascular closure device arena.

Aortic stenosis is a disease with a long latency period followed by rapid progression after the appearance of symptoms - approximately 50% of untreated patients will die within the first 2 years after symptoms appear.[7,8] Surgical replacement of the aortic valve in the absence of serious co-morbidities is associated with low operative mortality. However, approximately 30% of patients with severe symptomatic aortic stenosis do not undergo surgery due to advanced age, left ventricular dysfunction, and/or presence of multiple co-existing conditions.[4, 5] For these high-risk patients, a less invasive treatment, such as percutaneous aortic balloon valvuloplasty (BAV), introduced in 1985 by Dr. Cribier, is a less invasive alternative to surgical aortic valve replacement (SAVR) for severe aortic stenosis in high risk patients.[9] The procedure, generally carried out from a transfemoral artery approach, involves placement of one or more balloons across a stenotic valve followed by inflation to increase the aortic valve area.[10] Despite symptomatic benefit, early enthusiasm for BAV was tempered due to high restenosis rates and a failure to improve survival rates.[11, 12] Echocardiographic restenosis rates at 1 year were reported to be > 80% while mortalities ranged from 25-45%.[9] Over the last decade BAV is experiencing a resurgence largely due to improvements in BAV techniques, changing patterns and indications for use, and outcome improvements from initial reports.[8, 13]

The development of the TAVR/TAVI technique in clinical practice has also generated the need for VCD capable of accomplishing effective hemostasis after large diameter arteriotomies (up to 24Fr, recently down to 14Fr) as vascular access and closure remains a challenge.[14] Initially, open surgical access was routinely used to introduce large sheaths and catheters. Subsequently, percutaneous techniques have emerged as the new standard, resulting in a less invasive, fully percutaneous procedure.[15] One of the first reported randomized studies to compare the safety and efficacy of percutaneous access with surgical cutdown in transfemoral TAVR demonstrated no difference in the

primary endpoint of VARC-2 major and minor complications.[16] The overall rate of VARC-2 major vascular complications in the study was 13%. A recent meta-analysis of studies reporting on percutaneous (PC) versus surgical cut-down (SC) access in TAVR resulted in the inclusion of 2,513 patients in PC and 1,767 patients in SC.[17] Major and minor vascular complications, as well as bleeding complications, were comparable between the two approaches. The need for surgical intervention for vascular complications was comparable between PC and SC groups and there was no difference in perioperative all-cause mortality. The authors concluded PC and SC have similar safety profiles and outcomes when used appropriately in selected patients.

Minimally invasive approaches for the treatment of other forms of aortic pathology such as endovascular aortic repair procedures are now also very common. Endovascular aneurysm repair (or endovascular aortic repair/EVAR), is a type of endovascular surgery used to treat pathology of the aorta, most commonly an abdominal aortic aneurysm (AAA). EVAR, invented in the early 1990's, involves placing a stent graft into the aneurysm. Over the years the procedure has been refined to include new generation stent-graft and delivery systems. Studies have shown that patients treated with EVAR or traditional open surgery demonstrated fewer early complications with the minimally invasive approach and some studies have also observed a lower mortality rate with EVAR.[18, 19]

When used to treat thoracic aortic disease, the procedure is termed thoracic endovascular aortic/aneurysm repair (TEVAR). Originally developed by Dake in 1984 using the same principles as EVAR[20], TEVAR also involves the percutaneous placement of an expandable stent graft within the aorta.

1.2 Current Large Arteriotomy VCDs

Although BAV, TAVR/TAVI, EVAR, and TEVAR are less invasive alternatives to conventional surgical approaches, large sized delivery sheaths are still required. Management of the arterial access sites often represent a challenge and usually requires prolonged manual compression or alternatively suture-mediated closure techniques, two of which are commercially available. The Prostar XL was originally approved in the US and EU for closure of 5–8Fr access sites and has since gained a CE mark for up to 24Fr. The Perclose ProGlide® was originally approved for 5-8Fr and now is approved for up to 21Fr. The ProStar® XL, which provides four suture needles but, as

some have suggested, has a somewhat challenging platform, or two ProGlides placed at a 40º angle are placed at the beginning of the procedure leaving knots untied. The puncture site is then dilated to the appropriate size and the sutures are tied once the endovascular procedure is complete. For sheath sizes greater than 8Fr, at least two devices are required. More recently, a technique has been described using three ProGlides; this presumably grabs more segments of the arterial wall and provides redundancy in case one of the closures fails.[21] In the ProGlide® US FDA approval study, the majority of cases used two (74%) or three (18%) devices and some used four (4%) and five (2%) closure devices in the procedure.[22]

1.2.1 Clinical Experience With Suture-Based VCDs

Extensive published clinical experience with the suture based ProGlide and Prostar XL for percutaneous closure of large arterial access sites demonstrate relatively high rate of technical success and low access-related complication rates with ranges of 81-100% and 6-19% respectively.[15, 23-34] This data suggests that there is the possibility that use of the device in large arterial access sites could result in clinically meaningful savings in procedural time, patient recovery time and patient length of stay, which may lead to improved safety outcomes and reduced resource use as compared to surgical cut-down.[2, 19]

1.2.2 Advantages of Suture-based VCDs

Several advantages of suture-based closure devices have been suggested. An analysis of a database of 23,813 consecutive interventional coronary procedures that used either a collagen plug-based, nitinol clip-based or suture-based VCD, found that suture-based VCDs demonstrated a lower risk of vascular complications when compared with other VCDs irrespective of the success of VCD deployment. Although the collagen plug-based VCDs showed lowest failure rate (2.1%), when deployment was unsuccessful, it was associated with the highest vascular complication rate as compared to unsuccessful deployment of suture-based or nitinol clip-based VCDs. Deployment failure of suture based VCDs did not impact the vascular complication rate as compared with its successful deployment. It was proposed by the author that it was due, in part, to the availability of a “bailout” mechanism in the event of deployment failure that permits control of the arteriotomy site with sheath replacement or a second attempt at closure with VCDs. No bailout mechanism is readily available for the collagen plug-based or the nitinol clip-based VCDs.

Others have suggested percutaneous closure devices such as the Prostar XL might have advantages over surgical cut-down. The smaller scar reaction at the level of the groin increases the potential for repeat puncture of the femoral artery, allowing further vascular access when necessary.[2] Additionally, the complications associated with use of the Prostar® XL device, while similar in frequency to the rate of complications associated with surgical cut-down, can differ markedly in their seriousness and ease of resolution.[2]

1.3 Cross-Seal™ System and Indications For Use

The Cross-Seal™ System is indicated for the percutaneous delivery of sutures for closing the common femoral artery access site of patients who have undergone interventional catheterization procedures using 8Fr to 18Fr sheaths. The Cross-Seal™ System includes the Cross-Seal™ Device and three accessories (Cross-Seal™ Knot Tyer, Cross-Seal™ Knot Pusher, and Cross-Seal™ Suture Trimmer). The concept is similar to the suture-based VCDs described above but is designed to reduce the possible number of devices needed to close the arteriotomy and to reduce the steps required. One device deploys two (2) sutures in three (3) steps. Therefore, in addition to the aforementioned potential advantages of suture-based VCDs, other potential advantages of the Cross-Seal™ System include reduction in number of devices required and ease of use.

1.4 Description of Device

The Cross-Seal™ Suture Mediated Vascular Closure Device System (Cross-Seal™ System) includes the Cross-Seal™ Device and three accessories (Cross-Seal™ Knot Tyer, Cross-Seal™ Knot Pusher, and Cross-Seal™ Suture Trimmer). The Cross-Seal™ Device (**Figure 1**) is composed of a Catheter, Suture Delivery System and Handle. The device tracks over a standard 0.038” or 0.035” (minimum length 130 cm) guidewire. A HEMOSTASIS VALVE located in the middle of the CATHETER limits blood flow from the GUIDEWIRE PORT through the CATHETER with or without the guidewire in place. The Suture Delivery System contains NEEDLES, LOCATOR WINGS, and the NEEDLE BARREL that control suture placement around the arteriotomy. The Handle contains the SLIDER, BLEEDING INDICATOR, PLUNGER, RESET 1 BUTTON (SLIDER RETRACTOR), and RESET 2 BUTTON (LOCATOR WINGS RETRACTOR). The SLIDER triggers a mechanism that opens the LOCATOR WINGS and creates a sandwich configuration to stabilize the delivery system within the vessel wall. The

BLEEDING INDICATOR connects to a lumen that has an intraluminal port positioned at the distal end of the Suture Delivery System to allow back bleeding which ensures the Suture Delivery System is positioned properly in the femoral artery. The NEEDLE BARREL keeps the Cross-Seal™ Device from moving deeper inside the vessel, stabilizes the device once the LOCATOR WINGS are open and retrieves the disengaged suture-carrying NEEDLES. The PLUNGER triggers the NEEDLES to deploy the sutures and simultaneously closes the LOCATOR WINGS.

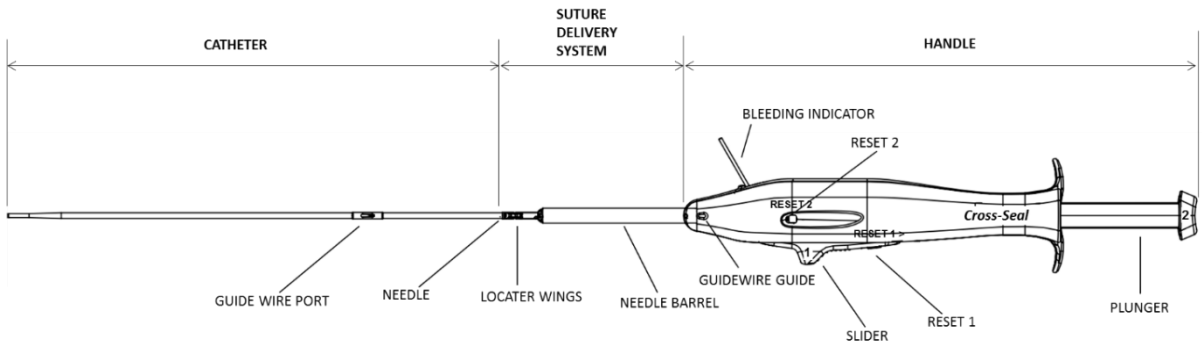

Figure 1: Cross-Seal™ Device

The Cross-Seal™ System includes the following three accessories:

1) **Cross-Seal™ Knot Tyer** is used to provide pre-tie fisherman's knots (also named Improve Clinch Knot) in the suture.
2) **Cross-Seal™ Knot Pusher** is used to advance pre-tied knots percutaneously to the top of the arteriotomy and secure the knots.
3) **Cross-Seal™ Suture Trimmer** is used to cut sutures after knots are delivered and secured to the top of the arteriotomy.

The Cross-Seal™ Knot Tyer (**Figure 2**) is used for making a Fisherman's knot.

- The TOP and SIDE HOOK are used to hook the two ends of suture.
- The RING TAB, which is connected to PRELOAD STRING, is pulled to trigger the process of making the knot. The non-rail end of suture will be brought into a preconfigured PRELOAD STRING on the ROTOR.
- The SLIDER is activated to release the loops and slide down the knot.

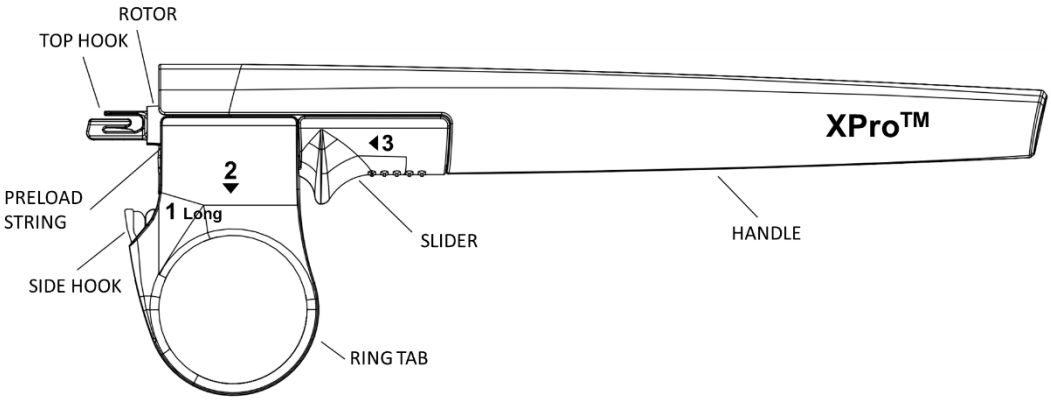

Figure 2: Cross-Seal™ Knot Tyer

The Cross-Seal™ Knot Pusher (**Figure 3**) is used for delivering the knot to the top of the arteriotomy. The SNARE WIRE is used to load the rail suture onto the PUSHER BODY, which is then pushed to advance the knot percutaneously to the top of arteriotomy.

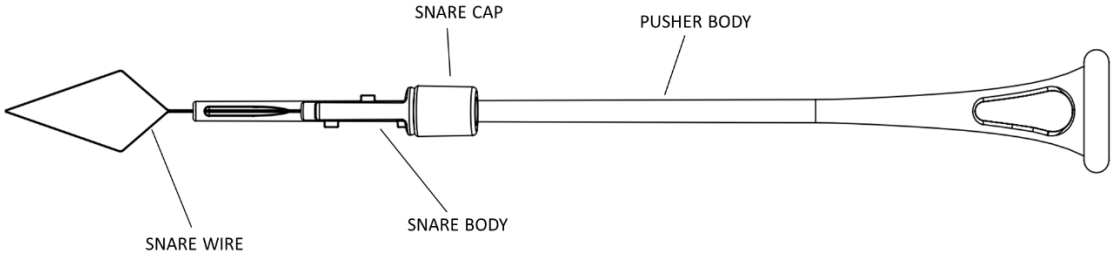

Figure 3: Cross-Seal™ Knot Pusher

The Cross-Seal™ Suture Trimmer (**Figure 4**) is used for trimming the suture ends percutaneously. The SLIDER controls the suture HOOK by advancing the HOOK for loading the sutures. The TRIGGER controls the cutting mechanism located at distal end of the CUTTING BARREL.

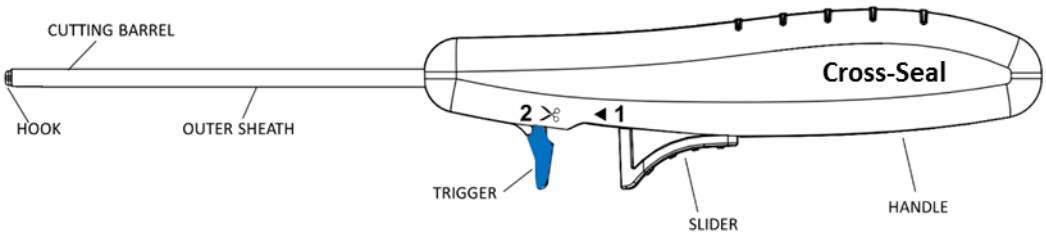

Figure 4: Cross-Seal™ Suture Trimmer

The Cross-Seal™ and Accessories are provided sterile to the user as single-use, disposable devices.

Cross-Seal™ System Specifications

Feature	Specification
Cross-Seal™ Device	
Guidewire Compatibility	0.038” or 0.035”
Catheter Diameter	9Fr
Interventional Device Compatibility	8-18Fr
Overall Device Length	555 mm
Catheter Length	232 mm
Locator Wings Length	17.4 mm
Needle Barrel Length	66 mm
Needle Barrel Outer Diameter	7 mm
Cross-Seal™ Knot Tyer	
Overall Device length	162 mm
Cross-Seal™ Knot Pusher	
Overall Device length	143 mm
Cross-Seal™ Suture Trimmer	
Overall Device length	185 mm

1.5 Summary of Clinical Studies

1.5.1 Clinical Feasibility (FIH) Study

A First-in-Human clinical study was conducted to assess the initial safety and feasibility of the Cross-Seal™ System GEN 1.0 to facilitate hemostasis in patients undergoing percutaneous transcatheter interventions involving access through the femoral artery using an 8-18Fr introducer sheath. Results are demonstrated as shown in **Table 1**. A total of ten (10) subjects were enrolled at a single site in Asuncion, Paraguay between October 26 and 27, 2015. A total of 10 patients completed the study. As shown in **Table 1**, the patient population consisted of 6 (60%) men and 4 (40%) women with a mean age of 66.0 years (range 56.3 to 80.2 years) and mean BMI of 29.2 kg/m^2 (range 24.2 to 36.7). The mean estimated diameter of femoral artery lumen at the closure site was 9.0 mm and ranged from 7.1 to 11.0 mm as measured via duplex ultrasound. Size 14Fr introducers were utilized in 2 patients and 18Fr introducers were used in 8 patients. The mean

Cross-Seal™ System procedure time was 4 minutes (range 1-8) and mean TTH was 3 minutes and 5 seconds (range 0-13:00). Total estimated blood loss including the interventional procedure was 97.2 mL (range 50-150). The mean Time-to-Ambulation was 3 hours and 12 minutes (range 1:25-9:12) and mean time-to-hospital-discharge was 18 hours and 17 minutes (range 14:05 to 22:22). Four adverse events occurred in 3 patients; 2 hematomas, 1 vessel spasm, and 1 post obstructive flow in the femoral artery. None of the adverse events were serious or unanticipated. All of the events reported were related to the procedure and not to the device and were resolved without any further action required. 100% of patients met the Cross-Seal™ System success defined as closure of the arteriotomy without the need for any access site related adjunctive surgical or endovascular procedures stemming from hemorrhagic, infectious, or ischemic complications. 100% of the patients met the primary and secondary safety endpoints - none had a major or minor vascular complication directly related to the Cross-Seal™ System as defined by VARC-2 (Valve Academic Research Consortium-2). The results of this feasibility study demonstrated that the Cross-Seal™ System is safe and performed as intended.

Table 1. Summary of First-In-Human Clinical Study of the Cross-Seal™ System (GEN 1.0)

Patient Population	
Gender	6 (60%) men and 4 (40%) women
Age	Mean age = 66.0 years (range 56.3 - 80.2 years)
BMI	Mean BMI = 29.2 (range 24.2 - 36.7)
Diameter of femoral artery lumen	Mean = 9.0 mm (range 7.1 - 11.0 mm)
Procedure	
Introducer size	14 Fr, n = 2 18 Fr, n = 8
Cross-Seal™ System procedure time	Mean = 4 minutes (range 1-8 minutes)
TTH	Mean = 3:05 minutes (range 0 - 13:00)
Total estimated blood loss	Mean = 97.2 mL (range 50-150 mL)
Technical Success	100%
Post-procedure	
Time-to-Ambulation	Mean = 3:12 hours (range 1:25-9:12)
Time-to-Hospital-Discharge	Mean = 18:17 hours (range 14:05 - 22:22)
Adverse Events	N = 3 patients; 2 hematoma, 1 vessel spasm, 1 post obstructive flow

1.5.2 CE Study

The CE study was a prospective, multi-center, and single arm study conducted in OUS countries. The primary endpoint of effectiveness was technical success defined as closure of the arteriotomy without the need for any access-site-related adjunctive surgical or endovascular procedures. The primary endpoint of safety was freedom from major VARC-2 events within 30 days of the procedure. Results are demonstrated as shown in **Table 2.**

A total of twenty-six (26) subjects were enrolled across 5 sites in Australia (1), New Zealand (3), and Taiwan (1), between May 30, 2017 and January 12, 2018. Study results from the total of 26 patients' data were monitored and shown in **Table 2**. The patient population consisted of 20 (77%) men and 6 (23%) women with a mean age of 76.5 years (range 33 – 91 years) and mean BMI is 25.7 (range 20.7-36.7). The mean estimated diameter of femoral artery lumen at the closure site was 8.3 mm and ranged from 6 mm to 11 mm as measure by ultrasound or CT scan. The introducer sheath utilized in study subjects ranged from 8Fr to 18Fr. An 8Fr introducer sheath was utilized in 1 (3.85%) subject, 9Fr introducer sheath was utilized in 1 (3.85%) subject, 10Fr introducer sheaths were utilized in 3 (11.54%) subjects, 12Fr introducer sheaths were utilized in 5 (19.23%) subjects, 14Fr introducer sheaths were utilized in 7 (26.92%) subjects, 16Fr introducer sheaths were utilized in 3 (11.54%) subjects and 18Fr introducer sheaths were utilized in 6 (23.08%) subjects. The mean TTH was 1 minute and 11 seconds (range 00:01 – 11:54). The mean estimated total blood loss including the interventional procedure was 158 ml (range 5 – 600 ml).

A successful ipsilateral "pre-close" percutaneous technique, defined as closure with the Cross-Seal™ System, was achieved in 100% of the subjects with no major ipsilateral access site vascular complication at 30 days follow-up.

Table 2. Summary of CE Clinical Study of the Cross-Seal™ System (GEN 2.0)

Patient Population	
Gender	20 (77%) men and 6 (23%) women
Age	Mean age = 76.5 years (range 33 - 91 years)
BMI	Mean BMI = 25.7 (range 20.7 - 36.7)

Diameter of femoral artery lumen	Mean = 8.3 mm (range 6.0 - 11.0 mm)
Procedure	
Introducer size	8 Fr, n = 1 9 Fr, n = 1 10 Fr, n = 3 12 Fr, n = 5 14 Fr, n = 7 16 Fr, n = 3 18 Fr, n = 6
TTH	Mean = 1:11 minutes (range 00:01 - 11:54)
Total estimated blood loss	Mean = 158 mL (range 5 -600 mL)
Technical Success*	100%
Post-procedure	
Adverse events	N = 12 subjects (35 adverse events) 1 Device related 1 Device probably related 33 Non-Device related

* In one case, user exceeded 90 degrees over guidewire and damaged the catheter, successful closure was achieved using a second device.

There were 35 adverse events which occurred in 12 subjects. Among the events, one is device related, one is probably device related, and 33 are non-device related. All adverse events related to access sites complications are in freedom from major VARC-2 events within 30 days of the procedure.

One (1) “device related” adverse event occurred as the operators passed the device between the catheter too quickly at > 90 degrees that led to pre-damage of the guidewire catheter port. The device was then withdrawn from the tortuous vessel resulting in catheter breakage. The broken portion was successfully removed and access site closure was achieved using a second Cross-Seal™ device. The IFU and training materials were updated accordingly to reinforce the importance of passing the device coaxially with an angle less than 60 degrees to prevent catheter bending or cracking. Additional on-site trainings were provided to the operators with agreement that under normal use conditions, catheter breakage should not occur. After training, no catheter bending or kinking was observed in the following 21 cases.

One “probably device related” adverse event, a small pseudoaneuysm, was observed. Such events are expected potential adverse events from suture-mediated vascular closure device.

Other adverse events related to access sites complications also were observed. They were non-occlusive thrombus and false aneurysm which are expected potential adverse events from suture-mediated vascular closure devices.
An independent Medical Monitor was appointed to review and adjudicate all SAEs that occurred during the course of the study. The results of this CE study demonstrated that the Cross-Seal™ System is safe and performed as intended.

In summary, the 10 subjects enrolled in FIH study and 26 subjects enrolled in CE study demonstrated a safety and effectiveness profile of Cross-Seal™ system. The patient population in the study underwent a variety of procedures including 19 BAV, 10 TAVI, and 7 TEVAR. The mean of TTH for total 36 subjects (FIH study and CE study) is 1 min 10 seconds. The mean TTH observed by sheath size are provided in **Table 3.**

Table 3. TTH vs Sheath Size in FIH Study and CE Study

	Cross-Seal™ System GEN 1.0, FIH Study		**Cross-Seal™ System GEN 2.0, CE Study**	
Sheath Size	**Closure Number**	**Mean TTH (min)**	**Closure Number**	**Mean TTH (min)**
8Fr	N/A	N/A	N=1	0.23
9Fr	N/A	N/A	N=1	0.63
10Fr	N/A	N/A	N=3	0.47
12Fr	N/A	N/A	N=5	0.55
14Fr	N=2	2.5	N=7	2.26
16Fr	N/A	N/A	N=3	1.95
18Fr	N=8	3.23	N=6	0.7
	Total (10)	**3.08**	**Total (26)**	**1.19**

2 Study Design, Sample Size and Duration

2.1 Study Design

This is a prospective, multi-center, single arm, clinical study to investigate the safety and efficacy of the Cross-Seal™ System.

The target population is comprised of subjects scheduled for elective percutaneous intervention with introducer sheath sizes of 8-18Fr and planned percutaneous arteriotomy closure. Applicable procedures include Transcatheter Aortic Valve

Replacement (TAVR), Endovascular Aneurysm Repair (EVAR). Thoracic Endovascular Aneurysm Repair (TEVAR) and Balloon Aortic Valvuloplasty (BAV).

2.2 Sample Size

A minimum of 3 sites and up to 25 sites in the US are expected to participate in the study with approximately 100 pivotal subjects enrolled. No more than 15% of the pivotal subjects may be enrolled at a single investigational site.

The first 1-2 subjects enrolled by each investigator will be considered roll-in subjects to allow for physician experience with the investigational device. A maximum of 3 study investigators and 6 roll-in subjects will be permitted at each investigational site.

In total, up to 250 subjects will receive the investigational device as part of the clinical study.

2.3 Study Duration

Study enrollment is expected to occur over a 10 to 12 month period. Imaging and follow-up procedures will continue through 30 days post-procedure. Subjects with an abnormal DUS at 30 days will have a repeat DUS at 60 days post-procedure (all DUS will be analyzed by an independent core laboratory). The total study duration is expected to be approximately 24 months.

Note: Due to the COVID-19 pandemic, some patient follow-up visits have been delayed greater than 6 months or completely missed; therefore, making data collection extremely difficult (e.g., missed DUS assessments) to support some of the secondary endpoints. To evaluate safety, we have added an unscheduled visit and telephone assessment (if needed) to be conducted as soon as possible based on physician and hospital regulatory discretion.

3 Study Objective, Hypothesis, and Endpoints

3.1 Study Objective

The study objective is to demonstrate the safety and efficacy of the investigational device to achieve hemostasis of common femoral artery access site in subjects undergoing percutaneous endovascular procedures utilizing 8-18Fr introducer sheath.

3.2 Study Hypothesis

Safety:

The freedom from major complications at the target limb access site within 30 days post-procedure will be greater than the specified PG.

Efficacy:

Following use of the investigational device, the mean TTH will be less than the specified PG.

3.3 Endpoints

This clinical study will evaluate the primary and secondary endpoints described below.

3.3.1 Primary Endpoints

Primary Safety Endpoint:

- Freedom from major complications of the target limb access site within 30 days post-procedure which includes the following:

Major Complications:

- Vascular injury attributable to the investigational device that requires surgical repair, stent-graft, or balloon angioplasty
- Access site-related bleeding attributable to the investigational device that requires transfusion
- Any new access site-related ipsilateral lower extremity ischemia attributable to the investigational device and documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram
- Surgery for access site-related nerve injury attributable to the investigational device
- Permanent (lasting > 30 days) access site-related nerve injury attributable to the investigational device
- Access site infection requiring intravenous antibiotics and/or extended hospitalization

Primary Efficacy Endpoint:

- The mean TTH in the Common Femoral Artery (CFA) of the target limb access site with use of the investigational device.

  TTH will be evaluated from time of procedural sheath removal to first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing at access site) in the target limb for subjects not requiring adjunctive intervention.

  If a sheathless system is used during the procedure, TTH will be calculated from final introducer sheath removal to first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing at access site) in the target limb for subjects not requiring adjunctive intervention.

  Adjunctive Intervention is defined as any use of surgical or endovascular intervention OR firm/occlusive manual pressure needed to achieve access site hemostasis (light/non-occlusive pressure to control cutaneous or subcutaneous oozing at the access site is excluded).

3.3.2 Secondary Endpoints

Secondary Safety Endpoints:

- The freedom from minor complications at the target limb access site within 30 days post-procedure which includes the following:

  Minor Complications:

  - Non-treated pseudoaneurysm attributable to the investigational device and documented by DUS
  - Pseudoaneurysm attributable to the investigational device and treated with ultrasound-guided compression, ultrasound-guided thrombin injection. or ultrasound-guided fibrin adhesive injection
  - Non-treated or treated arteriovenous (AV) fistula attributable to the investigational device and documented by DUS
  - Access site hematoma greater than or equal to 10 cm in diameter, attributable to the investigational device, and confirmed by DUS

  - Late (following hospital discharge) access site-related bleeding in target limb
  - Lower extremity arterial emboli attributable to the investigational device
  - Vein thrombosis attributable to the investigational device
  - Transient access site-related nerve injury attributable to the investigational device
  - Access site wound dehiscence
  - Access site infection treated with intramuscular or oral antibiotics
- Device Related Complications (DRCs) and procedural complications within 30 days post-procedure
- Evaluation of all Adverse Events (AEs) from time of investigational device use within 30 days post-procedure, and through 60 days post-procedure for subject's requiring a repeat DUS, including major and minor complications

Secondary Efficacy Endpoints:

- Technical Success: defined as achievement of hemostasis with the investigational device without the need for any access-site-related adjunctive surgical or endovascular intervention (target limb only).
- Access site closure success: defined as technical success and freedom from major complications within 48 hours of the index procedure or hospital discharge, whichever occurs first (target limb only).
- Treatment Success: defined as technical success and freedom from major complications through 30 days follow-up.
- Subjects requiring adjunctive surgical or endovascular intervention to achieve hemostasis of the access site (target limb only) including type of adjunctive intervention.
- Subjects receiving adjunctive manual compression following use of the investigational device to achieve hemostasis of the access site (target limb only).
  - Type of compression applied (light or firm, where light compression is defined as non-occlusive (i.e., "patent hemostasis") allowing distal blood flow, and firm compression defined as occlusive prohibiting distal blood flow.
- Time-to-Ambulation: defined as elapsed time from final procedural sheath removal to time when the subject stands and walks at least 20 feet without

re-bleeding.

- Time-to-Discharge (i.e., time of actual discharge defined as the elapsed time between final procedural sheath removal and when the subject is actually discharged from the hospital)
- Occurrence of device failure as defined in Section 13.0

3.3.3 Exploratory Endpoints

- Time-to-Device-Deployment defined as time of guidewire removal during device insertion to time of guidewire reinsertion during device removal, and overall procedure time defined as time of first skin nick/incision to achievement of hemostasis in the access site (target limb only)
- Time-to-Dischargeability (i.e., discharge eligibility defined as the elapsed time between final procedural sheath removal and time when the subject is medically able to be discharged based solely on the assessment of the access site as determined by the investigator.

4 Study Design

This is a prospective, multi-center, single arm, clinical study to investigate the safety and efficacy of the Cross-Seal™ System. The safety and efficacy will be evaluated immediately post-procedure, prior to hospital discharge, through 30 days post-procedure, and through 60 days post-procedure for subjects requiring a repeat DUS.

Study sites will make every attempt to conduct a telephone assessment for patients whose follow-up visits have been affected COVID-19. The assessment will evaluate AEs, concomitant medications and groin health status (which would otherwise be evaluated by a physical exam and DUS).

A subject is considered enrolled into the study if the subject has signed the ICF and meets all eligibility criteria.

4.1 Eligibility Criteria

Inclusion Criteria

1. Subject is ≥ 18 years old
2. Subject is scheduled for elective or planned (i.e., not emergent or urgent) percutaneous transcatheter interventional procedures involving access through

the femoral artery using 8-18 Fr introducer sheaths (i.e. BAV, TAVR/TAVI, EVAR, TEVAR)

3. Subject is able to undergo emergent vascular surgery if a complication related to the vascular closure necessitates such surgery
4. Subject is willing and able to complete follow-up requirements
5. Subject has the mental capacity to consent for themselves (i.e., does not require the use of a Legally Authorized Representative), and signs a written Informed Consent Form (ICF) prior participating in the study

Subjects will not be permitted to participate in the study if they meet any of the following general exclusion criteria and/or intra-procedure exclusion criteria:

General Exclusion Criteria

1. Prior intra-aortic balloon pump at access site
2. Subjects with severe inflow disease (iliac artery diameter stenosis > 50%) and/or severe peripheral arterial disease (Rutherford Classification 5 or 6), as confirmed with prior standard of care CT Imaging, duplex ultrasound, and/or intra-procedural fluoroscopy
3. Common femoral artery lumen diameter is < 5 mm
4. In opinion of the investigator, significant scarring of the target access site which would preclude use of the device in accordance with the IFU
5. Prior target artery closure with any closure device < 90 days, or closure with manual compression ≤ 30 days prior to index procedure
6. Prior vascular surgery, vascular graft, or stent in region of access site
7. Subjects receiving glycoprotein IIb/IIIa inhibitors before, during, or after the catheterization procedure
8. Subjects with significant anemia (Hgb < 10 g/dL, Hct < 30%)
9. Subject with known bleeding disorder including thrombocytopenia (platelet count < 100,000), thrombasthenia, hemophilia or Von Willebrand's disease
10. Subject with renal insufficiency (serum creatinine level > 221µmol/L or 2.5 mg/dL), on dialysis therapy, or with renal transplant
11. Known severe allergy to contrast reagent that cannot be managed with premedication
12. Inability to tolerate aspirin and/or other anticoagulation/antiplatelet treatment

13. Planned anticoagulation therapy post-procedure such that ACT is expected to be elevated above 350 seconds for more than 24 hours after the procedure
14. Connective tissue disease (e.g., Marfan's Syndrome)
15. Thrombolytics (e.g. t-PA, streptokinase, urokinase), Angiomax (bivalirudin) or other thrombin-specific anticoagulants ≤ 24 hours prior to the procedure
16. Recent (within 8 weeks) cerebrovascular accident or Q-wave myocardial infarction
17. Subjects who are morbidly obese (BMI > 40 kg/m^2)
18. Planned major intervention or surgery, including planned endovascular procedure in the target leg, within 30 days following the interventional procedure
19. Subject unable to ambulate at baseline (i.e., confined to wheelchair or bed)
20. Currently participating in a clinical study of an investigational device or drug that has not completed its primary study endpoint
21. Known allergy to any device component
22. Subject is known or suspected to be pregnant or lactating
23. Evidence of active systemic or local groin infection
24. Subject has other medical, social or psychological problem that in the opinion of the investigator precludes them from participating
25. Subject is mentally incompetent or a prisoner
26. New York Heart Association (NYHA) Class IV heart failure that is uncontrolled and requires treatment in the Intensive Care Unit within 24 hours prior to the index procedure
27. Left Ventricular Ejection Fraction (LVEF) < 20%
28. Unilateral or bilateral lower extremity amputation
29. Known existing nerve damage in the target leg
30. Subjects who have already participated in this IDE study

Intra-Procedure Exclusion Criteria

31. Access site above the most inferior border of the inferior epigastric artery (IEA) and/or above the inguinal ligament based upon bony landmarks
32. Access site in the profunda femoris or superficial femoral arteries, or the bifurcation of these vessels
33. Ipsilateral femoral venous sheath during the catheterization procedure
34. Common femoral artery calcium at the arteriotomy site (i.e., target access site), which is visible with prior CT Imaging and/or duplex ultrasound

35. Subject in which there is difficulty inserting the introducer sheath or need for greater than 2 ipsilateral arterial punctures at the start of the catheterization procedure
36. Difficulty in obtaining vascular access resulting in multiple arterial punctures and/or posterior arterial puncture
37. Evidence of a pre-existing hematoma (> 1.5 cm in diameter), arteriovenous fistula, pseudoaneurysm, or intraluminal thrombosis at the access site
38. Marked tortuosity (at the investigator's discretion) of the femoral or external iliac artery in the target leg based on prior CT imaging, fluoroscopy, and/or duplex ultrasound
39. Angiographic evidence of arterial laceration, dissection, or stenosis in the femoral artery that would preclude use of the investigational device
40. Target arteriotomy >18F sheath

The inclusion of subjects using other medications will be left to the discretion of the treating investigator. All such medication use, dose, and schedule will be recorded and documented.

4.2 Subject Enrollment

A minimum of 3 sites and up to 25 sites in the US are expected to participate in the study with approximately 100 pivotal subjects enrolled. No more than 15% of the pivotal subjects may be enrolled at a single investigational site.

The first 1-2 subjects enrolled by each investigator will be considered roll-in subjects to allow for physician experience with the investigational device. A maximum of 3 study investigators and 6 roll-in subjects will be permitted at each investigational site.

In total, up to 250 subjects will receive the investigational device as part of the clinical study.

5 Ethics

5.1 Role of the Sponsor

The Sponsor has the overall responsibility for the conduct of the study, including assurance that the study meets all regulatory requirements. In this study, the Sponsor

will have certain direct responsibilities and will delegate other responsibilities to the Clinical Research Organization (CRO). The Sponsor will conduct all its responsibilities in compliance with the Code of Federal Regulations (CFR).

5.2 Role of Clinical Research Organization

The Clinical Research Organizations (CROs) will support the data management and safety oversight throughout study conduct which includes, but is not limited to, safety review boards (DSMB, CEC), informing the Sponsor of any unanticipated adverse device effects (UADEs), serious adverse events (SAEs), and deviations from the protocol as appropriate. The CRO will conduct all its responsibilities in compliance with the Code of Federal Regulations (CFR).

5.3 Ethics Review

The final study protocol and written Informed Consent Form must be approved in writing by an Institutional Review Board (IRB). The principal investigator is responsible for informing the IRB of any amendments to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects to the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notification of serious, unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

5.4 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH/Good Clinical Practice, and applicable regulatory requirements.

5.5 Written Informed Consent

Written Informed Consent must be obtained prior to any study-related procedures*. The principal investigator will ensure that proper informed consent is provided, including ensuring the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified that they are free to discontinue/withdraw from the study at any time. The subject must be given the opportunity to ask questions and allowed time to consider the information

provided. The principal investigator will ensure that the subject has met all eligibility criteria prior to enrollment in the study.

The principal investigator must store the original, signed written ICF. A copy of the written ICF must be given to the subject. Any modifications made to the ICF must be approved by the IRB, Sponsor, and FDA if applicable.

**Pre-procedure assessments considered standard of care completed prior to obtaining informed consent do not need to be repeated if performed within 30 days of the procedure unless the investigator feels it is medically necessary, or unless otherwise specified (e.g., pregnancy test).*

5.6 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to the study Sponsor and or allow the Sponsor or their designate, a regulatory authority, or IRB access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

5.7 Subject Withdrawal

A subject's participation in the study is voluntary. Subjects may withdraw their consent from participation in the study at any time. A subject may withdraw completely or may withdraw but leave the authorization to access their medical records in effect. The investigator will take every reasonable measure to follow the subject for vital status and clinical events. Should a subject exit the study for any reason, the investigator will document the reason for study exit, if known, and record in the study database.

5.8 Discontinuing Subject Participation

A subject's continued participation in the study may be terminated for the following reasons:

1. Serious or severe adverse event or unanticipated adverse device effect.
2. Termination of study by the Sponsor.
3. Investigator determines that continued participation is not in the best interest of the subject.

4. Subject withdrawal of consent at any time.

6 Device Supply Information

6.1 Shipping

An initial supply of the investigational device will be shipped to investigational site when the site is approved by the Sponsor after all requirements, such as IRB approval and conduct of a Site Initiation Visit, are completed. Resupply of investigational devices during the study will be facilitated by the Sponsor, and/or designate.

6.2 Labeling

Labelling of investigational devices will be performed in accordance with the Good Manufacturing Practices (GMP) for Medical Devices of the Quality System Regulations (QSR). The devices will be packaged in individual trays with a peel-pack design. Each individual device tray will be packaged in a pouch within a cardboard box and will be labeled with the statement: "CAUTION Investigational Device. Limited by Federal Law to Investigational Use". Information on the investigational device label will indicate the identity, quantity, and storage conditions.

6.3 Storage

All investigational devices must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions will be specified on the device label and/or in the IFU. The stored device supplies must be accessible to authorized staff only, who must have adequate control of storage area temperature in order to maintain stability of the device supplies as specified in the IFU. The investigational devices should be stored in the original pack including tray, pouch, and box, until use. For further information, investigators should refer to the investigational device label and/or IFU.

6.4 Accountability

The investigator and delegated study personnel are responsible for maintaining accurate dispensing records of the investigational device. All devices must be accounted for, including devices accidentally or deliberately destroyed. All records for number of devices received, dispensed, and returned must be documented. Under no

circumstances will the investigator allow the investigational device to be used other than as directed by the protocol without prior Sponsor approval.

6.5 Return of a Malfunctioning/Failed Device

In the case where a device has malfunctioned and/or failed, the investigator must make every possible effort to return the device to the Sponsor, unless there is a known contamination with an infectious disease (i.e. Hepatitis B, C or HIV). Upon completion of the appropriate electronic Case Report Form (eCRF) for failed device, the Sponsor will contact the site with complete return instructions.

7 General Procedures

7.1 Baseline/Pre-Procedure Visit

Prior to the procedure, subjects must sign the informed consent form, meet all of the inclusion and none of the exclusion criteria and complete the following assessments:

The following baseline evaluations are required within 30 days prior to the Index Procedure unless otherwise specified:

- Informed Consent Form
- Eligibility Criteria
- Blood Tests including Complete Blood Count (CBC), Platelet Count, Serum Creatinine, Hemoglobin (HGB), Blood Urea Nitrogen (BUN), and Hematocrit (HCT) to assess eligibility criteria (collected within 2 weeks prior to index procedure)
- Medical History/Demographics
- Pregnancy test if female of child-bearing potential (within 7 days prior to procedure according to site standard of care)
- Target limb standard of care CT Imaging to document eligibility criteria requirements for CFA diameter and stenosis (performed up to 6 months prior to index procedure)
- Concomitant Medications (Anticoagulation / Antiplatelets Only)

Note: For subjects that do not have a standard of care CT Imaging modality, a micro puncture and angiogram intra-procedure, may be utilized to confirm eligibility criteria.

7.2 Index Procedure

Subjects that meet the general eligibility criteria and have signed the informed consent will have their scheduled interventional procedure (i.e., index procedure) performed in accordance with investigator/investigational site standard practices. Subjects on warfarin or anti-Xa inhibitors must be managed per institutional pre-interventional procedure standard of care.

Prior to the use of the investigational device, the investigator will assess the subject for the intra-procedure eligibility criteria to confirm enrollment in the study. If the subject is enrolled (i.e., signed informed consent and meets all eligibility criteria, including intra-procedural), the investigational device will be utilized for femoral artery closure according to the IFU. Enrolled subjects must also receive anticoagulant and/or antiplatelet medication during the index procedure in accordance with the IFU.

If the subject does not meet all eligibility criteria, the subject cannot be enrolled. The subject will be considered a screening failure and will not have the investigational device utilized. The investigator will perform the femoral artery closure according to their standard practice and the subject will not be followed as part of the study protocol. After completion of the interventional procedure, subjects will be treated in accordance with hospital standard of care and the study protocol.

Note: Only one single access site per subject will be eligible for use of the investigational device and any additional access sites will be managed according to the operator's standard of care. It is recommended the investigational device be used on the primary access site (i.e., ipsilateral) as on the side with the intended larger procedural sheath size. Should the procedure require a sheath that exceeds 18Fr at the primary access site (i.e., does not meet the eligibility criteria), the subject may still be enrolled if the secondary access site (i.e., contralateral to the primary access site) is within the acceptable range of 8-18Fr and meets the eligibility criteria.

At the end of the index procedure and prior to closure of the arteriotomy with the investigational device, the Activated Clotting Time (ACT) for heparinized subjects will be determined. It is required that the ACT < 350 seconds immediately prior to sheath removal to minimize the risk of bleeding; the investigator may use their standard of care and/or medication to control the ACT. In addition, if uncontrolled hypertension (systolic

blood press > 180 mm Hg or diastolic blood pressure > 110 mm Hg) or hypotension (Systolic blood pressure < 90 mm Hg) is observed just prior to planned vascular closure, every effort should be made to appropriately manage according to the investigator's standards of care.

After the vascular closure has been completed, cutaneous or subcutaneous oozing may be treated with light (non-occlusive) pressure applied to the access site manually, with a dressing, or as per the investigator's standard procedure for suture-mediated closure devices. Such oozing will not affect the TTH assessment or be considered an adverse event unless severe enough to require further treatment (i.e. surgery or other intervention). TTH, defined as elapsed time from procedural sheath removal to the first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing at access site), will be recorded. If a sheathless system is used during the procedure, TTH will be calculated from final introducer sheath removal to first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing at access site) in the target limb.

In the event of failure to achieve hemostasis following use of the investigational device and based on the investigator's assessment of bleeding, a bail-out method such as manual compression, compression assisted devices, secondary closure device and/or a surgical repair to obtain hemostasis should be performed according to the investigator's standard practice and the subject will be followed per the protocol. Should a secondary closure device be utilized for the bail-out method, it must be commercially available and cannot be the investigational device.

The following will be conducted during the index procedure:

- Eligibility Criteria (including intra-procedure)
- Femoral artery angiography to assess femoral artery and puncture site prior to utilizing the investigational device and after procedure for assessment of major and/or minor complications
- Activated Clotting Time (ACT)
- Time-to-Hemostasis (TTH)
- Concomitant Medications (Anticoagulation / Antiplatelets Only)
- Adverse Events (observed from time of enrollment)

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Table 2: Schedule of Events

Assessment	Screening / Baseline	Index Procedure	Post Procedure to Hospital Discharge	30 Day Follow-up	60 Day Follow-up∞	Unscheduled Visit ⁂
Informed Consent	X					
Eligibility Criteria	X	X				
Medical History/Demographics	X					
Pregnancy Test¶	X					
Blood Tests[μ]	X					
Femoral Artery Imaging (CT scan)– within 6 months prior to index procedure§	X					
Femoral Artery Angiography±		X				
Activated Clotting Time (ACT)		X				
Time-to-Hemostasis (TTH)≠		X				
Time-to-Ambulation†			X			
Time-to-Dischargeability‡			X			
Time-to-Discharge (TTD)¥			X			
Targeted Physical Exam, including groin exam				X	X	X[a]
Femoral Duplex Ultrasound (DUS)*				X	X	X[a]
Concomitant Medications (Anticoagulation / Antiplatelets Only)	X	X	X	X	X	X
Adverse Events ⌘		X	X	X	X	X
Phone Call assessment of AEs and patient condition						X

[μ] Blood Tests include Complete Blood Count (CBC), Platelet Count, Serum Creatinine, Hemoglobin (HGB), Blood Urea Nitrogen (BUN), and Hematocrit (HCT) to assess eligibility criteria (collected within 2 weeks prior to index procedure)
¶ Pregnancy test if female of child-bearing potential (collected within 7 days prior to index procedure according to site standard of care)
* Femoral Duplex Ultrasound is required for assessment of groin/access site related complications. If subject has an abnormal 30 day DUS, subject will be required to return for an additional DUS at 60 days post-index procedure.
§ Standard of care CT Imaging modality performed to assess femoral artery quality per trial criteria (collected within 6 months prior to index procedure). *Note: If subject does not have a previous CT imaging modality, a micro puncture and angiogram intra-procedure may be utilized to confirm eligibility criteria.*
± Femoral Angiography for assessment of quality of femoral artery and puncture site prior to utilizing investigational device.
⌘ Adverse events should be recorded at any time during the course of the study from time of enrollment through 30 days post-index procedure. Should a subject require a repeat DUS, AEs will be collected through 60 days post-index procedure.
† Time-to-Ambulation is defined as elapsed time from final procedural sheath removal and time when the subject stands and walks without re-bleeding.
‡Time-to-Dischargeability (i.e., discharge eligibility defined as the elapsed time between procedural sheath removal and time when the subject is medically able to be discharged based solely on the assessment of the access site as determined by the investigator.
¥Time-to-Discharge defined as the elapsed time between final procedural sheath removal and when the subject is actually discharged from the hospital
≠TTH will be evaluated from time of procedural sheath removal to first observed cessation of CFA bleeding (excluding cutaneous or subcutaneous oozing) in the target limb for subjects not requiring adjunctive intervention. If a sheathless system is used during the procedure, TTH will be from final introducer sheath removal to first observed cessation of CFA.
∞ 60 Day Follow-Up Visit assessments are only required if the subject returns to complete a repeat DUS following an abnormal 30 Day DUS
⁂ Unscheduled visits can occur at any time. Ensuring the safety of trial participants is paramount. Surveillance for adverse events and concomitant medications can be collected via telephone contact or similar if the patient is unable to make an in-person visit.
[a] If clinically indicated.

7.3 Investigational Device Set-up and Preparation

Please refer to the IFU for additional guidance for the investigational device.

7.4 Concomitant Medical Therapy

Subjects enrolled in this study should be medicated according to investigator's standard of care prior to, during, and after the interventional procedure. Enrolled subjects must also receive anticoagulation and/or antiplatelet medication during the index procedure in accordance with the IFU.

Any medications should be recorded on the appropriate eCRF.

7.5 Follow-up Procedures

Subjects will be evaluated prior to discharge and through 30 days post-procedure. Subjects with an abnormal 30 Day DUS will be required to complete a repeat DUS at 60 days post-procedure. All follow-up visit dates will be calculated based on a 30 day calendar.

7.5.1 Post-Procedure through Hospital Discharge

The subject may ambulate or be discharged when clinically stable, at the investigator's discretion.

The following information will be collected from procedure through hospital discharge:

- Time-to-Ambulation, defined as elapsed time from final procedural sheath removal to time when the subject stands and walks at least 20 feet without re-bleeding
- Time-to-Dischargeability, i.e., discharge eligibility defined as the elapsed time between procedural sheath removal and time when the subject is medically able to be discharged based solely on the assessment of the access site as determined by the investigator
- Time-to-Discharge (i.e., time of actual discharge defined as the elapsed time between final procedural sheath removal and when the subject is actually discharged from the hospital)
- Concomitant Medications (Anticoagulation / Antiplatelets Only)
- Adverse Events

7.5.2 30 Day Follow-Up (30 ± 7 days)

All subjects will be asked to return to the investigational site 30 days post-procedure. This visit will conclude the subject's participation in the study unless the subject has an abnormal 30 day DUS in which case the subject will return for a repeat DUS at 60 days post-procedure.

The following data will be collected:

- Femoral Duplex Ultrasound (DUS) for assessment of groin/access site related complications (target limb only)
- Targeted physical exam, including groin exam
- Concomitant Medications (Anticoagulation / Antiplatelets Only)
- Adverse Events

7.5.3 60 Day Follow-Up (60 days ± 14 days)

All subjects with an abnormal DUS at 30 days post-procedure will be asked to return to the investigational site at 60 days post-procedure to complete a repeat DUS.

The following data will be collected:

- Repeat DUS for assessment of groin/access site related complications (target limb only)
- Targeted physical exam, including groin exam
- Concomitant Medications (Anticoagulation / Antiplatelets Only)
- Adverse Events

7.5.4 Unscheduled Visit

The unscheduled visit is designed to evaluate the ongoing safety of enrolled patients outside the protocol defined 30-day and/or 60-day visits.

Patients with missed or incomplete in-person protocol defined visits due to the COVID-19 pandemic will not be considered lost-to-follow-up/withdrawn by the Sponsor. Rather, the unscheduled visit can be used to reconsent the patient for this extended follow up to

evaluate their safety. The Interim follow up visit will be available for up to 12 months from the primary study index procedure and subjects should return as soon as reasonably possible unless the patient wishes to be withdrawn from the study.

The following data will be collected during the unscheduled visit:

- DUS for assessment of groin/access site related complications in target limb only (if not completed already or if repeat is needed (e.g., missed 30-day and/or 60-day visit))
- Targeted physical exam, including groin exam (if not completed already or if repeat is needed (e.g., missed 30-day and/or 60-day visit))
- Concomitant Medications (Anticoagulation / Antiplatelets Only)
- Adverse Events

If the patient will not or cannot return for an unscheduled visit, the study site should contact the patient via telephone to determine AEs and patient condition.

7.6 Clinical Data Collection

Information about subject demographics, eligibility requirements, procedure summary, concomitant mediations as well as any procedure complications and/or adverse events will be collected on eCRFs provided by the Sponsor. The eCRFs should accurately reflect data contained in the subject's medical records (i.e. source documents).

8 Adverse Events

The reporting and recording of adverse events is crucial to the evaluation of an investigational device, and to the development of labeling information that appears in the IFU. During a clinical study, the reporting of adverse experience information can lead to important design changes in the new device, as well as provide integral safety data. The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the procedure.

Subject safety will be monitored via the reporting of adverse events occurring from the time of enrollment through study completion. Any pre-existing condition known to the investigator will not be reportable as an adverse event unless that condition worsens during the study.

Where an adverse event has, by its nature, a prolonged course, the event will be considered a single event and not multiple events. For example, if a subject develops end-stage renal failure requiring regular dialysis, the event is considered as end stage renal failure, not multiple single renal events.

The investigator is not obligated to actively seek adverse events from a subject once a subject has completed/exited the study. If the investigator learns of any adverse event at any time after a subject's exit from the study, and there is a reasonable possibility that it is related to investigational device, the investigator should promptly report it to the Sponsor.

8.1 Definitions

An *adverse event* (AE) is defined as an unwanted medical occurrence in a subject. This definition does not imply that there is a relationship between the AE and the device under investigation. This can include, but is not limited to, a change in the subject's health status from baseline that is related to the disease process, interventional procedures, investigational device, and/or side effects to medications.

An *adverse device effect* is defined as those adverse events that are caused by, or related to, the investigational device.

An *unanticipated adverse device effect* (UADE) is an adverse device effect that is not described in the study risk assessment or the informed consent. "Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

A *serious adverse event* (SAE) is an adverse event that led to a death or led to a serious deterioration in the health of a subject that:

1. Resulted in a life-threatening illness or injury,
2. Resulted in a permanent impairment of a body structure or body function,

3. Required in-subject hospitalization or prolongation of existing hospitalization,
4. Resulted in medical or surgical intervention to prevent impairment to body structure or a body function, or
5. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Each AE will be assessed by the investigator to determine whether it is serious or non-serious. (Note: The term serious is not synonymous with severity, which is used to describe the intensity of an event experienced by the subject).

A *serious adverse device effect* is an adverse event that is both serious and device related.

8.2 Potential Adverse Events (AEs)

Potential complications associated with the investigational device as with all other suture mediated closure devices may include, but are not limited to, the following:

- Allergic reaction or hypersensitivity to device components
- Anemia
- Arterial stenosis/occlusion
- Arteriovenous fistula
- Bleeding/hemorrhage
- Bruising
- Death
- Deep vein thrombosis
- Device entrapment
- Device failure/malfunction/misplacement
- Diminished pulses distal to closure site
- Embolism
- Extended Hospitalization / Delayed time to ambulation
- Hematoma
- Infection/sepsis

- Inflammation
- Intimal tear/dissection
- Ischemia distal to closure site
- Nerve injury
- Numbness
- Pain
- Perforation
- Pseudoaneurysm
- Retroperitoneal hematoma/bleeding
- Superficial vein thrombosis
- Surgical exposure/closure of common femoral artery
- Thrombus formation
- Vascular injury
- Vasovagal episode
- Vasoconstriction/vasospasm
- Wound dehiscence

8.3 Follow-up of Adverse Events

All adverse events observed from the time of enrollment throughout the duration of the study must be reported on the eCRF. All adverse events will be followed until resolution or stabilization of symptoms through study completion and/or the subject withdraws consent. Resolution means that the subject has returned to a baseline state of health. Stabilization means that the investigator does not expect any further improvement or worsening of the adverse event.

8.4 Causality Rating

The causal relationship of an adverse event to the investigational device will be rated as follows:

Not Related: An event for which an alternative explanation is conclusively identified - e.g., concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is highly unlikely.

Possible: An event that is unlikely due to the use of the investigational device. An alternative explanation - e.g., concomitant drug(s), concomitant disease(s) - is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable: An event that might be due to the use of the investigational device. An alternative explanation is less likely - e.g., concomitant drug(s), concomitant disease(s). The relationship in time is suggestive.

Definitely: An event that is due to the use of the investigational device. The event cannot be reasonably explained by an alternative explanation - e.g., concomitant drug(s), concomitant disease(s).

8.5 Severity of Adverse Events

The severity of an AE will be rated as follows:

Mild	An adverse event that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities.
Moderate	An adverse event that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe	An adverse event that prevents normal everyday activities; treatment or other intervention usually needed.

8.6 Events Requiring Expedited Reporting

Expedited Events refer to events that the site principal investigator should report to the CRO/Sponsor within twenty-four (24) hours of knowledge of the event. The appropriate eCRF and related documents should be completed in the data management system.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be reported using the appropriate eCRF.

The Sponsor will immediately conduct an evaluation of any unanticipated adverse device effects (UADEs). If the effect is determined by the Sponsor to present an unreasonable risk to the subject, all investigations or parts of the investigation presenting that risk will be

terminated as soon as possible. Termination will occur not later than five working days after the Sponsor makes this determination, and not later than 15 working days after first receiving notice of the effect.

The Sponsor will not resume an investigation terminated under these conditions without an additional IRB approval.

8.6.1 Expedited Events include:

1. Unanticipated Adverse Device Effects (as defined in section 8.1) will include events meeting either A or B as stated below:

A. Events meeting ALL of the following criteria:

- Not included in the list of Anticipated Events (refer to section 8.2)
- Possible, probable, or definitely related to the investigational device per the site principal investigator
- Serious (meets any of the following criteria):
    1. Resulted in a life-threatening illness or injury
    2. Resulted in a permanent* impairment of a body structure or body function
    3. Required in-patient hospitalization or prolongation of existing hospitalization
    4. Resulted in medical or surgical intervention to prevent impairment to body structure or a body function

*(Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage)

B. Any other unanticipated serious problem associated with the investigational device that relates to the rights, safety, or welfare of subjects

2. Device Failures as defined in Section 13
3. Device Malfunctions as defined in Section 13
4. User Errors: A device is used by the investigator in a manner that is contrary to the IFU
5. All Deaths

8.7 Clinical Events Committee (CEC)

The CEC is composed of physicians who are interventional and/or non-interventional cardiologists, who are not participating in this study, and who do not have any investment with the study Sponsor. The CEC is charged with the review and classification of adverse events (AEs), including deaths. The CEC will establish rules outlining the minimum amount of data required and the algorithm followed in order to classify AEs. All members of the CEC will meet regularly to review and classify AEs. All appropriate data will be reviewed by the CEC. The CEC will forward a report of event reviews and classifications as outlined in the CEC charter.

8.8 Data and Safety Monitoring Board (DSMB)

The DSMB will be appointed to monitor the conduct of the study and subject safety by periodically reviewing data from the study. The DSMB will oversee the overall safety of current and future study subjects by protecting them from avoidable harm. The DSMB will review adverse events and other relevant study data and will recommend study termination if safety concerns warrant such action. The DSMB will also establish guideline criteria for recommending study termination, to the extent possible that the DSMB can predict adverse events or outcomes, before the proposed study begins.

The DSMB will be an independent committee with no direct involvement in the day-to-day undertaking of the study and no investment in the Sponsor. DSMB members and activities may overlap with the CEC as appropriate. The DSMB will consist of physicians, including one chairperson and a statistician who will provide an independent review of the data. The physicians will include an interventional cardiologist and vascular surgeon experienced in vascular closure to ensure appropriate review of vascular complications in the study. The DSMB report will detail all serious and unexpected adverse events or other unanticipated problems that involve potential risk to future study participants. If the DSMB has concerns regarding the study, the DSMB will notify the Sponsor, who will provide the relevant summaries to local IRBs. Actions taken by any IRB in response to safety concerns will be reported to the DSMB.

The DSMB will meet periodically throughout the study in order to assure close and timely monitoring of adverse events and outcomes. The operational details of the DSMB will be determined early in the study and formalized in the DSMB Charter.
The Sponsor and/or CRO will be responsible for working with the DSMB to ensure the DSMB Charter is developed. After the DSMB Charter has been finalized and approved by the DSMB, any changes or deviations to the plans in the charter will be documented in the minutes of the DSMB meetings.

Reports will be prepared by the Sponsor and/or CRO as requested by the DSMB Chairman and as required per the charter. In addition to safety data, the reports may include recruitment and retention rates, interim analyses and other information as requested by the DSMB Chairperson.

9 Risk Assessment

9.1 Risk Management Procedure

Subjects will be monitored closely throughout the study duration. Risks will be further mitigated through selection of qualified physicians, appropriate training, and study monitoring ensured by the following:

- Investigators who participate in the study will be experienced and skilled in endovascular techniques. Additionally, investigators, in conjunction with the investigational site, will have adequate resources for participation in a clinical study.
- The study has been designed to ensure treatment and follow-up of subjects are consistent with current medical practice.
- Each investigator will ensure oversight and approval of the study by their IRB prior to initiation of the clinical study at his/her investigational site.
- The investigator and study personnel will be trained on the clinical protocol and IFU for the investigational device.
- Subjects will be carefully evaluated against the eligibility criteria prior to entering the clinical study to ensure that their diagnosis and medical status are appropriate for participation.

- Subjects will be monitored throughout the follow-up period as defined in the study protocol. Subjects will have visits with the investigator or his/her designee to monitor the subjects' status pre-procedure, intra-procedure, and post-procedure.
- A DUS will be performed at 30 days post-procedure and repeated at 60 days if subject had an abnormal 30 day ultrasound to ensure adequate evaluation of the target limb access site.

9.2 Potential Benefits

Subjects enrolled in this clinical study will be monitored closely throughout the study and have regular assessments according to the investigator's standards of care. The data collected during the clinical study will provide further understanding how the Cross-Seal™ System is clinically beneficial. Potential benefits may include:

- Reduced Time-to-Ambulation (TTA)
- Reduced Time-to-Hemostasis (TTH)
- Improved quality of life

10 Centers for Medicare and Medicaid Services (CMS) Reimbursement

The Sponsor will seek applicable Medicare coverage in compliance with CMS requirements for this study. Based on the target study population including mean age, approximately 70% of subjects enrolled in this study will utilize CMS/Medicare reimbursement during their participation.

The study will be conducted in compliance with all applicable Federal regulations concerning the protection of human subjects found at 21 CFR parts 50, 56, and 812, and 45 CFR part 46. In addition, the study will be registered with the National Institutes of Health National Library of Medicine's ClinicalTrials.gov.

The Sponsor has a legal responsibility to the regulatory authorities to fully report all results of sponsored clinical studies. No investigational procedures other than those in this protocol shall be undertaken. The sponsor intends to submit a formal report to FDA following completion of the last subject visit required for primary endpoint analysis. Should the study be terminated early, the Sponsor will make every effort to expedite reporting of study

results to the FDA database for public review. Any use of the investigational device by an investigator that is contradictory to the application described in the IFU will be categorized as device misuse.

11 Monitoring

The Sponsor will perform monitoring functions within this clinical study and may be delegated to a CRO designate as needed. Study monitors will work in accordance with standard operating procedures (SOPs) and the approved Monitoring Plan. Any CRO monitors have the same rights and responsibilities as monitors from the Sponsor organization.

At the site, monitors will perform and verify the following:

- The adequacy and experience of the study center including Sponsor notification of any problems relating to facilities, technical equipment or medical staff
- Written Informed Consent has been obtained from all subjects prior to any study related procedures being performed and that data is recorded correctly and completely
- Source Document Verification (SDV): comparing data in the eCRFs to ensure they correspond with applicable source data, and to inform the Sponsor and investigator of any discrepancies, errors or omissions
- Ensure adherence to the protocol and applicable regulations at the investigational site and notify the Sponsor promptly of any deviations
- Evaluate subject compliance and support subject retention efforts at the site
- Device accountability and appropriate storage conditions are maintained according to the IFU

Data will be collected using eCRFs for this study. Investigative sites will enter data directly into the eCRFs via a web-based system. A Sponsor representative will provide training and technical assistance to the investigator and site staff on the procedural application, intended use, and performance characteristics of the investigational device. In addition, a Sponsor representative will schedule periodic, on-site visits to observe clinical procedures, under

supervision of the investigator, and to answer questions or concerns regarding the investigational device.

Given that on-site monitoring at some trial locations may be impacted due to the COVID-19 pandemic, the Sponsor has implemented both central and remote monitoring to maintain oversight of the clinical study and sites. This includes, but is not limited to, telephone and/or email contacts with the sites (to review study procedures, trial participant status, and study progress), remote review of de-identified source, remote access to electronic medical records (EMR), and frequent eCRF reviews. Given the ongoing and unpredictable nature of the COVID-19 pandemic, individual site variability on permitting remote EMR and/or the transmission of de-identified source, as well as continually changing local and state mandates governing travel, the Sponsor may have to adapt its monitoring processes regularly to fulfill its obligations as a Sponsor under federal law and regulations. The Sponsor will continuously assess each site and will monitor study data at the earliest possible opportunity, either in person or remotely.

12 Image Analysis

Duplex Ultrasound (DUS) of the femoral artery will be obtained at 30 days post-procedure (target limb only). In the instance of an abnormal DUS at 30 days, the subject will be required to conduct a repeat DUS at 60 days post-procedure.

All Duplex Ultrasound images obtained during the study will be anonymized and sent to a central core laboratory for independent analysis.

13 Device Failure and Malfunction

A device failure has occurred when the device is used in accordance with the IFU, but does not perform as described in the IFU, and also negatively impacts treatment of the study subject. Device Failures may include the following:

- Device used in study subject resulting in the occurrence of a major complication
- Unable to use RESET 1 Button
- Unable to deploy PLUNGER on device
- Unable to use RESET 2 Button

A device malfunction occurs when the device is used in accordance with the IFU and an unexpected change to the device contradictory to the IFU is observed, which may or may not affect device performance. Device Malfunctions may include the following:

- Device(s) with which insertion attempts were made, but was not used in the subject.
- Unable to observe bleeding back after sufficient dissection is performed
- Unable to deploy slider of Cross-Seal™ Device
- Needle dislodged after device deployment
- Unable to cut suture with Suture Trimmer
- Device is damaged in packaging
- Issues with use of Knot Tyer and/or Knot Pusher
- Suture break during device, Knot Tyer and/or Knot Pusher use
- Device packaging issue
- Device Sterility issue

Device malfunctions occurring in roll-in subjects will be additionally evaluated for potential relationship with the learning curve of the investigational device (e.g., operator applies excess tension to suture during pre-closure causing break)

In the case where a device has malfunctioned/failed, the investigator must make every possible effort to return the device to the Sponsor, unless there is a known contamination with an infectious disease (i.e. Hepatitis B, C or HIV).

14 Statistical Methods

14.1 Sample Size Determination

The sample size calculations were performed using PASS 2020 Version 20.0.2[iii]. The appendix included the output from the software. The sample size for the study is based on power considerations for the primary effectiveness endpoint. As will be described below, this sample size should also provide adequate power for the primary safety endpoint.

14.1.1 Primary Efficacy Endpoint

The primary effectiveness hypothesis will be tested by comparing the primary effectiveness endpoint, mean time-to-hemostasis (TTH), against a performance goal (PG) of 15 minutes.

The comparison to the performance goal will be based on the following statistical hypothesis test:

$$H_O: \mu_{TTH} \geq 15$$

$$H_A: \mu_{TTH} < 15$$

where $\mu_{TTH}$is the mean time-to-hemostasis in minutes.

The test will be based on whether the upper one-sided 97.5% confidence limit (based on a t-distribution)[iv] is less than 15. Assuming similar performance to Perclose ProGlide®, with a mean time-to-hemostasis of 9.8 minutes and a standard deviation of 17 minutes the sample sizes for power levels from 80 to 90%

a Table 3: Primary Efficacy Endpoint Sample Sizes for Various levels of Power

Power	Sample Size	Maximum Observed Time (minutes) and still reject H_0
80.0%	86	10.8
81.4%	89	10.9
82.3%	91	10.9
83.1%	93	10.9
84.3%	96	11.0
85.0%	98	11.1

Successful rejection of the null hypothesis will mean that the PG has been met.

14.1.1.1 Development of the Performance Goal

The PG was derived from literature for the Perclose ProGlide® (Abbott Vascular, Inc., Redwood City, CA, USA), a suture-mediated device indicated for the closure of large arterial access sites.

14.1.2 Primary Safety Endpoint

The primary safety hypothesis will be tested by comparing the primary safety endpoint, freedom from major complications of the target limb access site within 30 days post-procedure, against a performance goal.

The comparison to the performance goal will be based on the following statistical hypothesis test:

$$H_O: p \leq 85.2\%$$

$$H_A: p > 85.2\%$$

where p is the safety endpoint rate for the test device.

Assuming similar performance as ProGlide (an event-free rate of 94%), one-sided alpha = 0.05, the sample sizes for various levels of power are:

Table 4: Primary Safety Endpoint Sample Sizes for Various levels of Power

Power	Sample Size	Minimum # of Event Free Patients needed to reject the H_0
81.3%	78	72
85.6%	86	79
88.3%	95	87

14.1.2.1 Development of the Performance Goal

The observed rate of major complications for ProGlide was 6% (3/50), with a one-sided exact binomial upper 95% confidence bound of 14.8%. In terms of an event-free rate, these quantities are mathematically equivalent to an observed event-free rate of 94%

with a lower confidence bound of 85.2%. Accordingly, for the current study, a value of 85.2% is proposed for a performance goal for the primary safety endpoint based on the event-free rate.

14.2 Statistical Analyses

14.2.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analyses will be conducted using {SAS version 9.3 or later (SAS Institute Inc., Cary, NC)} or other widely accepted statistical or graphical software as required.

14.2.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and exact binomial method for categorical variables.

14.2.1.2 Study Visit

Study visit Day 0 is the date of the index procedure. Day in the study will be calculated relative to the index procedure as follows:

Study Day = Assessment Date – Index Procedure Date

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

Duration will be calculated as follows: Duration Days = Start Date – End Date

14.2.1.3 Visit Windows

Unless otherwise specified, visit assessments will be analyzed for each analysis time point according to the visit entered in the electronic Case Report Form (eCRF).

14.2.1.4 Statistical Significance

Unless otherwise specified, hypothesis testing will be performed at the two-sided 0.05 significance level. P-values will be rounded to three decimal places. If a p-value is less

than 0.001 will be reported as "<0.001". If a p-value is greater than 0.999, it will be reported as ">0.999".

14.2.1.5 Reporting Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places. For continuous parameters, means and medians will be reported to 1 additional decimal place than the measured value. In contrast, the standard deviation will be reported to 2 additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

14.2.2 Analysis Populations

14.2.2.1 Full Analysis Set

The full analysis set (FAS) as defined by the ICH E9[v] as "The set of subjects that is as close as possible to the ideal implied by the intention-to-treat principle." The guideline also defined the Intention-To-Treat Principle as the effect of a treatment policy can be best assessed by evaluating based on the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given. Therefore, the FAS includes all patients that were consented, enrolled, and met the inclusion/exclusion criteria.

14.2.2.2 Per-Protocol Analysis Set

The protocol definition of the TTH endpoint includes only those patients that received the test device and did not have adjunctive therapy other than light compression applied to the access site manually, with a dressing, or as per the investigator's standard procedure for suture-mediated closure devices. Therefore, the per-protocol analysis set (PPS) includes those patients in the FAS where the patient received the test device and did not have adjunctive therapy other than light compression.

14.2.2.3 Full Roll-In Analysis Set

The full roll-in analysis set (FAS_RI) are those patients that meet the same criteria as the FAS but are identified as roll-in patients.

14.2.2.4 Per-Protocol Roll-In Analysis Set

The per-protocol roll-in analysis(PPS_RI) set are those patients that meet the same criteria as the PPS but are identified as roll-in patients.

14.2.2.5 Efficacy Analysis Set

Due to the challenges during the pandemic, the number of patients in a non-missing primary efficacy endpoint may drop below the lowest accepted power (80%) for approval trial design (< 86 patients). If the number of patients in the PPS is <= 86, the efficacy analysis set will include the patients in the PPS and the last 18 sequentially enrolled patients from the PPS_RI. If the number of patients in the PPS is > 86, then the efficacy analysis set will only include PPS patients.

14.2.2.6 Safety Analysis Set

Due to the challenges during the pandemic, the number of patients in a non-missing primary safety endpoint may drop below the lowest accepted power (80%) for approval trial design (< 78 patients). If the number of patients in the FAS is <= 78, the safety analysis set will include the patients in the FAS and the last 18 sequentially enrolled patients from the FAS_RI. If the number of patients in the FAS is > 78, then the safety analysis set will only include FAS patients.

14.2.3 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary endpoints will be presented separately (major and minor complications will be presented separately for the primary safety endpoint) for each site using descriptive statistics. Poolability of the primary endpoints across the investigational site will be evaluated using a regression model with fixed effects for the site using the FAS for the primary safety endpoint and PPS for primary efficacy endpoint. Sites enrolling less than five subjects will be combined with the geographically nearest site. If the p-value for the site effect is <0.15, additional exploratory analyses will be performed to understand any variations in outcomes by site.

14.2.4 Handling of Missing Data

All attempts will be made to limit the amount of missing data. For all analyses of the primary endpoints, the number of observations available, patients with no primary safety endpoint information, and patients with imputed results will be reported so the reader can assess the impact of missing data.

14.2.5 Imputation for Endpoints

Due to the challenges related to the COVID-19 pandemic faced during the enrollment, some 30-day follow-up visits were outside of the protocol specified window. Therefore, for those patients whose 30-day visit was outside the window, the primary safety endpoint will be imputed based on the on visits that occurred at a minimum of 23 days post-discharge and is the closest to the 30-day visit. If there were no post-discharge visits, the primary safety endpoint will be imputed based on the site contacting the patient by phone as well as reviewing their records to determine the patient's primary safety endpoint status at 30 days. If even that information is not available, then the patient will be considered as missing the primary safety endpoint data.

14.2.6 Sensitivity Analyses

Sensitivity analyses will be performed to assess the impact of missing data for the primary safety endpoint; a tipping point analysis will be conducted in which subjects censored without a 30 days follow-up visit are sequentially imputed as failures at the time of censoring. The primary safety endpoint analysis will be repeated after each sequentially imputed failure.

Sensitivity analyses will be performed to assess the impact of missing data for the primary efficacy endpoint; a tipping point analysis will be conducted in which subjects without a TTH are sequentially imputed as 15 minutes (the performance goal). The primary efficacy endpoint analysis will be repeated after each sequentially imputed value.

14.2.7 Imputation for Dates

More generally, in the case of partial adverse event onset date or date of death, the unknown portion of the date of the event will be imputed. If the month and year are known, the 15th of the month will be used for analysis. If only the year is known, the event will be analyzed as if it occurred on June 30th of the known year. In the rare case that the date is fully unknown, the date will be imputed as the index procedure date. Imputation of partial dates is subject to the condition that it must occur on or after the index procedure date. In the case where the imputed date is before the index procedure date, the date of the index procedure will be used. As death cannot occur before any documented subject contact, for date of death, the imputed date of death must occur on

or after the last known contact in the study.

14.2.8 Subject Disposition

Subjects who are screened and signed an informed consent form, but do not meet all protocol eligibility criteria (i.e., screening failure), will be excluded from the statistical analyses. These subjects will be summarized in a subject accountability table only.

Subject accountability will be summarized by visit for those in the FAS. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit.

14.2.9 Demographics and Baseline Characteristics

Descriptive statistics will be presented for clinically relevant baseline demographic, medical history, and clinical characteristic variables.

14.2.10 Analysis of Study Endpoints

Study success is defined as the successful rejection of the corresponding null hypotheses for each of the primary safety and effectiveness endpoints.

14.2.10.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be evaluated using the using the efficacy analysis set. The mean and standard error will be reported for the primary efficacy endpoint. A one-sample t-distribution will be used for calculating the upper 97.5% confidence limit.

14.2.10.1.1 Sensitivity Analyses

There will be three sensitivity analyses:

1. The primary efficacy endpoint analysis will be repeated with the PPS patients only if PPS_RI patients are added to the efficacy analysis set
2. Tipping analysis based on missing data in the efficacy analysis set as described in section 14.2.6
3. The primary efficacy endpoint analysis will be repeated with the PPS_RI and the efficacy analysis set combined.

14.2.10.2 Primary Safety Analysis

The primary safety endpoint will be evaluated using the FAS or the safety analysis set if roll-ins are needed. The endpoint will be presented as the proportion of subjects with

freedom from primary safety endpoint and the lower 95% confidence limit using the Clopper-Pearson exact method[vi]. If the one-sided 95% confidence limit is greater than 85.2%, then the device will have met the performance goal for safety.

14.2.10.2.1 Sensitivity Analyses

There will be three sensitivity analyses:

1. The primary safety endpoint analysis will be repeated with the FAS patients only if FAS_RI patients are added to the safety analysis set
2. Tipping analysis based on missing data in the safety analysis set, as described in section 14.2.6.
3. The primary efficacy endpoint analysis will be repeated with the FAS_RI and the safety analysis set combined.

14.2.10.3 Secondary Endpoints

No formal hypothesis tests for the secondary and exploratory endpoints will be performed; endpoints will be summarized using the FAS with descriptive statistics.

14.2.11 Subgroup Analyses

Subgroup analysis of the primary safety (major and minor complications analyzed separately) and efficacy endpoints will be performed for the following subgroups: gender, age (Age<65, Age≥65), and race (white vs. non-white). These analyses are intended to assess the consistency of results across subgroups.

Subgroup analyses will be performed using the efficacy analysis set for the primary efficacy endpoint and the safety analysis set for the primary safety endpoint. For each subgroup, a regression model will be fit that includes fixed effects for subgroup membership.

14.2.12 Interim Analyses

There are no formal plans for interim analyses for the purposes of early stopping for effectiveness or sample size adjustments. Interim safety reports will be performed as requested by the DSMB Charter. Unless otherwise specified, methods for such reports may follow those outlined in this document.

14.2.13 Protocol Deviations

Investigational sites will report deviations from the procedures outlined in the CIP on the eCRF. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

14.2.14 Additional Changes to Planned Analyses

Any additional changes to planned statistical analyses determined necessary before performing the analyses will be documented in an amended Statistical Analysis Plan Version 1.4 and approved before the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

15 Reporting

A final integrated clinical/statistical report will be prepared and provided to the FDA for the purposes of fulfilling the requirements of the IDE and PMA submission.

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