E7116

A Multicenter, Single-Arm Study of Endoscopic Ultrasound-Guided Drainage of Walled-off Pancreatic Necrosis with Lumen-Apposing Metal Stents

AXIOS WON Drainage IDE

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Protocol

August 16, 2018

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AXIOS WON Drainage IDE (E7116)

Clinical Investigation Plan

IDE# G170261

Sponsored By

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Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
92153943, Rev/Ver. B	October 6, 2017	Template 90702637 Rev/Ver AH	4.3	Changed header to Additional Endpoints; added additional endpoint #7 from Synopsis	Typo
92153943, Rev/Ver. B	October 6, 2017	Template 90702637 Rev/Ver AH	7.2	Deleted the Sample Size section as it already resides under Section 7.1	Typo
92153943, Rev/Ver. B	October 6, 2017	Template 90702637 Rev/Ver AH	15.1	Removed Complete Distal Migration from the last bullet and replaced with Necrosectomy Procedure	Typo
92153943, Rev/Ver. C	October 10, 2017	Template 90702637 Rev/Ver AH	7.3	Sample Size relocated within Section 7	Administrative
92153943, Rev/Ver. D	November 1, 2017	Template 90702637 Rev/Ver AH	7.1	Added Success Criteria	Per FDA Feedback
92153943, Rev/Ver. D	November 1, 2017	Template 90702637 Rev/Ver AH	7.2	Added Success Criteria and Table 7.3 of categorized SAEs from recent literature	Per FDA Feedback
92153943, Rev/Ver. E	November 21, 2017	Template 90702637 Rev/Ver AH	Synopsis, 5.2	Addition of exclusion criteria #6	Per FDA Feedback
92153943, Rev/Ver. E	November 21, 2017	Template 90702637 Rev/Ver AH	Synopsis, 6.1, 6.4	Addition of the collection of current medication	Per FDA Feedback
92153943, Rev/Ver. E	November 21, 2017	Template 90702637	15.1	Language added to clarify that BSC	Per FDA Feedback

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
		Rev/Ver AH		will be responsible for all UADE assessments	
92153943, Rev/Ver. F	December 14, 2017	Template 90702637 Rev/Ver AH	Synopsis, 5,7	Changed sample size to 40, added random-effects meta-analysis for resolution rates and SAE rates, modified success criteria. Changed title of "Safety Cohort" to "Treated Cohort"	Per FDA Feedback
92153943, Rev/Ver. G	May 9, 2018	Template 90702637 Rev/Ver AJ	Synopsis, Visit Schedule Safety Endpoint 6.4, 2.1, 7.2	Added Imaging criteria to Study Visits and Synopsis; added labs to screening/pre-op visit; removed clinical UPNs; protocol template update, added safety endpoint assessment to synopsis and safety endpoint; added procedural details to stent placement visit and synopsis; Made changes to the primary effectiveness endpoint assessment; Added section 7.2 Safety Endpoint Assessment; added SF-12 to Appendices	Per Site/Investigator Feedback
92153943, Rev/Ver. H	August 15, 2018	Template 90702637 Rev/Ver AJ	7.4	Added double pigtail plastic stents to justification of pooling	Per FDA Feedback

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
92153943, Rev/Ver. I	**August 16, 2018**	**Template 90702637 Rev/Ver AJ**	**Synopsis, 6.3, 7.4**	**Added Boston Scientific 7Fr Advanix™ Biliary Stent to Stent Placement Procedure**	**Per FDA Feedback**

Protocol Synopsis

Full Title	**A Multicenter, Single-arm Study of Endoscopic Ultrasound-Guided Drainage of Walled-off Pancreatic Necrosis with Lumen-Apposing Metal Stents**
Short Title	AXIOS™ WON Drainage IDE
Study Objective	To demonstrate safety and effectiveness of lumen-apposing metal stents for resolution of walled off pancreatic necrosis (WONs) in patients with WONs with solid component >30%
Indication(s) for Use	Current cleared indication for use: The AXIOS™ Stent and Electrocautery Enhanced Delivery System is cleared in the U.S. "for use to facilitate transgastric or transduodenal endoscopic drainage of symptomatic pancreatic pseudocysts ≥ 6cm in size and walled-off necrosis ≥ 6cm in size with ≥ 70% fluid content that are adherent to the gastric or bowel wall. Once placed, the AXIOS™ Stent functions as an access port allowing passage of standard and therapeutic endoscopes to facilitate debridement, irrigation and cystoscopy". Outside the U.S., the AXIOS™ Stent and Electrocautery Enhanced Delivery System is indicated for use to facilitate transgastric or transduodenal endoscopic drainage of a pancreatic pseudocyst or walled-off necrosis with ≥ 70% fluid content or to facilitate drainage of the biliary tract. Proposed expanded indication for this IDE study: The AXIOS™ Stent and Electrocautery Enhanced Delivery System is intended "for use to facilitate transgastric or transduodenal endoscopic drainage of symptomatic pancreatic pseudocysts ≥ 6cm in size and walled-off necrosis ≥ 6cm in size that are adherent to the gastric or bowel wall. Once placed, the AXIOS™ Stent functions as an access port allowing passage of standard and therapeutic endoscopes to facilitate debridement, irrigation and cystoscopy".
Test Device	AXIOS™ Stent and Electrocautery Enhanced Delivery System
Test Device Sizes	10mm, 15mm, and 20mm
Study Design	Prospective, single arm, multi-center trial
Number of Subjects	40
Number of Sites	Up to 6 centers

Primary Endpoints	Primary Effectiveness Endpoint: Resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI Primary Safety Endpoint: AXIOS™ stent related or WON drainage procedure related serious adverse events
Additional Endpoints	1. Reduction of WON-related clinical symptoms. *Note: WON-related symptoms as defined in Inclusion Criteria #4* 2. Technical AXIOS™ stent placement success, defined as placement in desired location using endoscopic/EUS techniques per standard of practice. 3. Technical AXIOS™ stent removal success, defined as ability to remove the AXIOS™ stent using an endoscopic snare or forceps or graspers without AXIOS™ stent removal related serious adverse events. 4. Drainage procedural time: Time elapsed between initial puncture of the WON with electrocautery to endoscope retrieval. 5. Resolution of WON with or without necrosectomy by 6 months post AXIOS™ stent removal. 6. Time to WON resolution using same definition as for primary endpoint, namely: • Resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI 7. Recurrence of WON after initial resolution and up to 6 months post AXIOS™ stent removal. 8. Stent lumen patency, evaluated via imaging or direct visual inspection with endoscope, and defined as one or both of the following: • Drainage through AXIOS™ stent visualized from the stomach or bowel, and/or • Visual confirmation of AXIOS™ stent lumen patency 9. Fluoroscopy (time) per endoscopic procedure. 10. Incidence of new organ failure from drainage procedure to WON resolution. 11. Change in Quality of Life score (SF-12 questionnaire) from baseline to stent removal and end of study

Study Visits and Follow-Up Schedule	• Screening/ Pre-op Visit: informed consent, demographics, etiology of Acute Pancreatitis (biliary, alcohol, idiopathic or other), onset date of AP, WON related symptoms, baseline CT scan or MRI (identification of % necrosis and confirmation of absence of pseudoaneurysms inside WON), organ failure assessment (Marshal scoring system), severity of AP, and Quality of Life (SF-12), labs, current medication • Stent Placement Procedure: o AXIOS™ stent placement *Note: Physicians will select the site of the AXIOS™ stent placement under endoscopic guidance and choose an access location that is free from necrotic debris and intervening blood vessels, where the wall between the GI tract and fluid collection is 10mm or less, and where it is possible to place the AXIOS™ stent in a position such that the inner flange (inside WON) has enough space to expand.* o Lavaging of WON and/or breaking up of large chunks of necrosis under endoscopic visualization for up to 20 minutes, and/or placement of nasocystic drain, or a single 7fr double pigtail plastic stent (Boston Scientific 7Fr Advanix™ Biliary Stent) through the AXIOS™ stent at the discretion of investigator. o Stent lumen patency assessment o Adverse event/device event assessment o Current medication o Labs (as needed) *Note: Labs need to be repeated at this visit ONLY IF they were collected more than 3 days before the stent placement procedure.* • WON Resolution Assessment Visit - 7 days (+/-3 days) for inpatients and 14 days (+/- 5 days) for outpatients (needed until radiographic decrease of WON size to ≤ 3cm): o Cross sectional imaging (CT or MRI) to assess reduction in WON size. If reduction in size is deemed insufficient, necrosectomy will be initiated o Documentation of clinical improvement defined as improvement of principal WON-related symptoms o Necrosectomy (as needed) o Adverse event/device event assessment)

	○ Organ failure assessment (Marshal scoring system) ○ Current medication ○ Labs (as needed) • <u>Reintervention/Necrosectomy Visits when needed during AXIOS™ stent indwell:</u> ○ Necrosectomy initiated if WON reduction in size is deemed insufficient during WON Resolution Assessment Visit. Duration of each necrosectomy session is limited to 60 minutes ○ Percutaneous drainage or additional endoscopic drainage may be needed if reduction in WON size is insufficient or in cases of continued WON related symptoms such as infection/sepsis despite necrosectomy. Choice of stent (AXIOS™ or double pigtail plastic stent(s)) for repeat endoscopic drainage procedures will be left to the discretion of the investigator. The double pigtail plastic stent(s) or new AXIOS™ stent may be placed through the tract established by the original AXIOS™ stent or in a separate location. ○ Stent lumen patency assessment ○ Adverse event/device event assessment ○ Labs (as needed) ○ Imaging (as applicable) ○ Current medication • <u>Stent Removal Visit - between 14 days and 60 days of stent placement</u>: ○ Stent lumen patency assessment ○ Stent removal after evidence of clinical and radiographic (via CT or MRI) resolution of WON *Note: Removal of stent by 60 days is required if WON is not resolved. Patients with unsuccessful or incomplete WON resolution by 60 days will proceed to standard of care treatment outside of this protocol after removal of the AXIOS™ stent; however, the patient outcome will continue to be followed. Alternative interventions may include surgery, endoscopic drainage with double pigtail plastic stents, percutaneous catheter drainage and necrosectomy (video-assisted retroperitoneal debridement (VARD), or endoscopic transluminal debridement, or open necrosectomy).*

	○ Adverse event/device event assessment ○ Organ failure assessment (Marshal scoring system) ○ Quality of Life (SF-12) ○ Current medication • <u>7 Day (+/- 3 days) Post Stent Removal Visit – (office or phone call):</u> ○ Adverse Event assessment ○ Current mediation • <u>WON Recurrence Assessment Visit/End of Study - at 6 Months (+/- 14 days) from stent removal:</u> ○ Recurrence assessment (presence of clinical symptoms and further diagnosis per standard of care (e.g. labs and imaging) ○ Adverse Events assessment ○ Quality of Life (SF-12) ○ Current medication

Key Inclusion Criteria	1. Age between 22 and 75 years old 2. Severe or moderately severe acute necrotizing pancreatitis, defined per the 2012 Revised Atlanta Classification [1]. 3. WON resulting from necrotizing pancreatitis per contrast-enhanced CT or MRI with the following characteristics, per the 2012 Revised Atlanta Classification: [1]. • Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous) • Well defined wall • Location-intrapancreatic and/or extrapancreatic 4. Infected WON or symptomatic sterile WON *Note: WON-related symptoms may include: pain, fever, leukocytosis, failure to thrive or deterioration of overall heath score, gastric outlet obstruction (GOO), weight loss, biliary obstructive symptoms, systemic inflammatory response syndrome (SIRS), deteriorating organ function, chronic nausea, lethargy, and inability to eat or gain weight* 5. Imaging suggestive of greater than 30% necrotic material 6. WON ≥ 6cm in size 7. Eligible for endoscopic intervention 8. Acceptable candidate for endoscopic transluminal drainage 9. Patient understands the study requirements and the treatment procedures and provides written Informed Consent 10. Patient is willing to comply with all specified follow-up evaluations, including willingness to undergo a pre/post imaging study

Key Exclusion Criteria	1. Pseudocyst 2. Cystic neoplasm 3. Untreated Pseudoaneurysm > 1cm within the WON 4. More than one WON clearly separated and requiring drainage 5. WONs that require dual modality interventions (endoscopic and percutaneous) from the beginning (i.e. deep paracolic space involvement that is inaccessible through the central drainage access) 6. Prior surgical, interventional radiology or endoscopic procedures for the treatment of the WON 7. Abnormal coagulation: • INR > 1.5 and not correctable • presence of a bleeding disorder • platelets < 50,000/mm^3 8. Intervening gastric varices or unavoidable blood vessels within the access tract (visible using endoscopy or endoscopic ultrasound) 9. WON that poorly approximates the GI lumen (≥1cm away) 10. Pericolic gutter necrosis 11. Pelvic necrosis 12. Prior true anaphylactic reaction to contrast agents, nitinol (nickel titanium), silicone or any other materials contacting the patient 13. Female of childbearing potential with a positive pregnancy test prior to the procedure or intends to become pregnant during the study 14. Currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study
Multiple Interventions During Index Procedure	<u>Index Procedure:</u> Once stent is placed into the WON, dilation of the AXIOS™ stent is allowed to expand the stent if needed. Dilation can be performed to the maximal diameter of the AXIOS™ stent. A single, 7 fr double pigtail plastic stent (Boston Scientific 7Fr Advanix™ Biliary Stent) may be placed through the AXIOS™ stent at the discretion of the investigator. Access to the WON with a forward viewing diagnostic or therapeutic upper gastroscope is allowed up to 20 minutes (from time of endoscopic access of the WON) to break-up large chunks of necrosis and lavage collection at the discrection of the physician.

Primary Effectiveness Endpoint Assessment	*Note: Success will be based on the number of WONs resolved, not on the number of AXIOS™ Stents required to achieve resolution.* • If it is determined that the fluid collection is actually two separate collections, and each collection is drained via an AXIOS™ stent, then each collection will be assessed individually via the drainage success criteria of ≤3cm. • If it is determined that the fluid collection is a single collection but the drainage is inadequate via a single AXIOS™ stent, then the success of the AXIOS™ drainage will be assessed as follows: o If a second AXIOS™ stent is used at a new drainage site/original drainage site and the entire fluid collection is drained to meet the success criteria of ≤3cm then the collection will be considered to be a single collection drainage success. o If a second AXIOS™ stent is used at a new drainage site and the entire fluid collection does not drain adequately to meet the drainage success criteria of ≤3cm then the fluid drainage of the collection will be considered to be a single drainage failure. o If a plastic stent is used at a new drainage site and the entire fluid collection drains to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered indeterminate o If a single, 7fr plastic stent is used at the same drainage site, through the AXIOS™ stent, and the entire fluid collection drains to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered a single collection drainage success. o If a plastic stent is used at a new drainage site and the entire fluid collection does not drain to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered a single drainage failure.

Primary Safety Endpoint Assessment	The Primary Safety Endpoint is AXIOS™ stent related or WON drainage procedure related serious adverse events however if it is determined that the patient has an infection, then the primary safety success of the AXIOS™ device or the drainage procedure will be assessed as follows: • If the patient presents with an infected collection at the initial drainage procedure, the infection will be classified as a localized infection and will not be considered a stent related or WON drainage related serious adverse event • If the patient presents with a sterile collection at the initial drainage procedure and post-procedurally develops an infected collection, the infection will be classified as a localized infection and will not be considered a stent related or WON drainage related serious adverse event as this is a known consequence of any endoscopic drainage procedure, where the access route to the collection is through a non-sterile GI lumen and is not a function of a particular stent or device (*Note: If the stent is occluded at the onset of infection, then the infection will be attributed to the device. If the stent remains unobstructed at the time of infection, then the infection will not be attributed to the device.)* • If the patient presents with a sterile or infected collection at the initial drainage procedure and then post-procedurally develops a wide-spread infection in the form of sepsis or blood stream infection, then the infection will be classified as systemic and will be considered a stent related or WON drainage related serious adverse event only if the AXIOS stent was clearly and visually occluded by solid necrosis at the time of repeat endoscopy. This determination will be made by the operating physician at the time of endoscopy
Statistical Methods	

Primary Effectiveness Endpoint – Statistical Methods	As in the original IDE, #G130264, there is no formal statistical hypothesis for this study. The proportion of AXIOS patients with reduction of WON size to ≤ 3cm within 60 days from AXIOS™ stent placement in the original IDE is 76.7% (23/30) patients. Given that the WONs in the proposed IDE will have an estimated necrotic material content above 30%, namely larger than in IDE #G130264, a slightly lower success rate of 70.0% is expected for this study. This success rate is within the range of reported WON resolution rates in several recent publications [2-8] on plastic stent WON drainage, an established WON drainage method as described in the ASGE guidelines on treatment of pancreatic fluid collections [9].
Primary Effectiveness Endpoint – Success Criteria	An observed rate of 67% or higher for the proportion of AXIOS™ patients with reduction of WON size to ≤ 3cm within 60 days from AXIOS™ stent placement is required for success.
Primary Safety Endpoint – Statistical Methods	As in the original IDE, #G130264, there is no formal statistical hypothesis for this study. The proportion of AXIOS™ patients with AXIOS™ stent related or WON drainage procedure related serious adverse events in the original IDE is 10.0% (3/30) patients. A similar rate of AXIOS™ stent related or WON drainage procedure related serious adverse events is expected in this study. This event rate is within the range of reported stent related or WON drainage procedure related serious adverse event rates in several recent publications [3-5, 10] on plastic stent WON drainage, an established WON drainage method as described in the ASGE guidelines on treatment of pancreatic fluid collections [9].
Primary Safety Endpoint – Success Criteria	An observed rate of 17.5% or lower for the proportion of AXIOS™ patients with AXIOS™ stent related or WON drainage procedure related serious adverse events is required for success.
Sample Size – Statistical Methods	The sample size of 40 patients was determined without statistical consideration based on previous clinical experience showing adequate effectiveness and safety with a similar sample size.

Table of Contents

1 Introduction

Walled-off pancreatic necrosis (WON) is a late complication of acute pancreatitis. Annually there are about 185,000 cases of WON that occur in the U.S, and the majority (at least 80%) are caused by alcohol and cholelithiasis [11].

WON was formerly known as pancreatic abscess and in 2012, the Atlanta Classification system for pancreatitis was revised to update the terminology used to classify pancreatic fluid collections (PFCs) in an attempt to provide better clinical guidance on diagnosis and treatment of pancreatitis [12]. The revised classification introduced new terminology for the various types of PFCs that are based on the timing of the development of the collection into the clinical course of the disease, as well as on the presence or the absence of necrosis in the PFC. Fluid collections developing prior to 4 weeks are called acute peripancreatic fluid collections or acute necrotic collections. Once the collection develops a contrast-enhancing capsule, which usually occurs after 4 weeks, fluid collections are called either pseudocysts (no necrotic material present) or walled-off necroses (WONs) if necrotic material is present. Any of these PFC types can be sterile or infected according to the revised Atlanta Classification.

When PFCs become infected or symptomatic, drainage procedures are performed. Currently, drainage can be accomplished surgically, via percutaneous interventional radiology techniques, or endoscopically [13-15]. Surgery for PFCs is associated with relatively high rates of morbidity (7-37%) and mortality (6%) [16], and it has been reported that percutaneous drainage increases the risk of infection and the formation of pancreaticocutaneous fistulae [17, 18]. As a result, endoscopic drainage techniques have replaced surgery and percutaneous drainage techniques as the first-line therapy for symptomatic PFCs because they have high technical and clinical success rates with lower rates of complications, shorter recovery times, and lower cost [18, 19]. The most common type of endoscopic drainage procedure is the endoscopic ultrasound-guided transmural approach. During this type of procedure, the PFC is accessed via creation of a tract between the PFC and the lumen of the stomach or duodenum and a drainage device is placed through this tract. The device connects the interior of the PFC with the lumen to allow internal drainage. Double-pigtail plastic stents (usually 7-10F in size) and fully-covered, self-expanding metal stents (usually those designed for the biliary tract) are used as the drainage device [20-23]. However, both of these stent types are associated with problems. While the double-pigtail design of the plastic stents tends to prevent migration, the narrow lumen of these stents tends to occlude quickly, particularly in the drainage of WONs where solid necrotic material may be present within the collection in addition to fluid [19, 24]. This necessitates multiple stent exchanges or placement of additional stents. The metal biliary stents offer a larger-diameter lumen and longer patency, but because they have a tubular design they can migrate quickly, resulting in poor drainage, leakage, and mucosal injury in the digestive tract [25].

Recently, the use of "barbell" shaped lumen-apposing, fully covered self-expanding metal stents such as the AXIOS™ stent for drainage of WONs has been reported. These large-diameter stents may provide better drainage of both fluid and solid material from the WON with less chance of stent occlusion, and the flanges on this type of stent may prevent stent

migration by apposing the WON wall to the stomach or duodenal wall. This could result in faster resolution of the WON using fewer endoscopic procedures. Rinninella et al, performed a retrospective study examining the drainage of PFCs, including WON. They included 93 patients with PFCs (80% with complex collections) who underwent drainage with AXIOS™, 52 of whom had WON. Among those with WON, the solid component was judged to be less than 25% of the collection in 14 patients, between 25% and 50% in 20 patients, and more than 50% in the remaining 18 patients. Clinical success, resolution of PFCs without the need for additional endoscopic or percutaneous drainage procedures or surgery, was achieved in 47 of 52 patients (90.4%) with WON [26]. A separate study performed by Shah et. al. prospectively analyzed patients with chronic pancreatitis who received treatment of pancreatic pseudocysts or WONs using AXIOS™. They concluded that the large lumen size of the metal stent allows for successful necrosectomy through the stent when needed [27].

The current study is proposed to supplement this literature by documenting the safety and effectiveness of the AXIOS™ lumen apposing self-expandable metal stent system for the drainage of WON containing greater than 30% necrotic material.

2 Device Use and Description

2.1 *Device Description and Device Use*

Study devices are manufactured by Boston Scientific Corporation. The AXIOS™ Stent is a flexible, fully-covered self-expanding metal stent that is preloaded within the Electrocautery-Enhanced Delivery System. The stent is made of Nitinol and fully-covered with silicone. The AXIOS™ Stent and Electrocautery-Enhanced Delivery System is compatible with therapeutic echoendoscopes having a working channel of 3.7mm diameter or larger.

Current cleared indication for use: The AXIOS™ Stent and Electrocautery Enhanced Delivery System is cleared in the U.S. “for use to facilitate transgastric or transduodenal endoscopic drainage of symptomatic pancreatic pseudocysts ≥ 6cm in size and walled-off necrosis ≥ 6cm in size with ≥ 70% fluid content that are adherent to the gastric or bowel wall. Once placed, the AXIOS™ Stent functions as an access port allowing passage of standard and therapeutic endoscopes to facilitate debridement, irrigation and cystoscopy. The stent is intended for implantation up to 60 days and should be removed upon confirmation of pseudocyst or walled-off necrosis resolution.” Outside the U.S., the AXIOS™ Stent and Electrocautery Enhanced Delivery System is indicated for use to facilitate transgastric or transduodenal endoscopic drainage of a pancreatic pseudocyst or walled-off necrosis with ≥ 70% fluid content or to facilitate drainage of the biliary tract.

Proposed expanded indication for this IDE study: The AXIOS™ Stent and Electrocautery Enhanced Delivery System is intended “for use to facilitate transgastric or transduodenal endoscopic drainage of symptomatic pancreatic pseudocysts ≥ 6cm in size and walled-off necrosis ≥ 6cm in size that are adherent to the gastric or bowel wall. Once placed, the AXIOS™ Stent functions as an access port allowing passage of standard and therapeutic endoscopes to facilitate debridement, irrigation and cystoscopy.”

The study device is not approved for drainage of WONs with greater than 30% necrotic material and will be considered investigational for this indication. Local Institutional Review Board (IRB)/ Ethics Committee (EC) approval will be obtained at each participating center.

Study devices are labeled on the box and inner pouch and include information not limited to name of legal manufacturer, device name and dimensions, lot number, expiration date and investigational use statement. Device labeling will be provided in local language(s) as per national regulations. Devices will be available in the following matrix:

Table 2.0-1: Device Matrix

Description	Stent Size			Delivery System Outer Diam.
	Lumen Diameter	Saddle Length	Flange Diameter	
Electrocautery Enhanced AXIOS™ System with 10x10 Stent	10 mm	10 mm	21 mm	10.8Fr
Electrocautery Enhanced AXIOS™ System with 15x10 Stent	15 mm	10 mm	24 mm	10.8Fr
Electrocautery Enhanced AXIOS™ System with 20x10 Stent	20 mm	10 mm	29 mm	10.8Fr

For a detailed description of the AXIOS™ Stent and Electrocautery-Enhanced Delivery System, please reference the Investigator's Brochure.

3 Study Objective

To demonstrate safety and effectiveness of lumen-apposing metal stents for resolution of WONs in patients with WONs with solid component >30%.

4 Endpoints and Study Design

4.1 *Primary Effectiveness Endpoint*

Resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI.

4.2 *Primary Safety Endpoint*

AXIOS™ stent related or WON drainage procedure related serious adverse events.

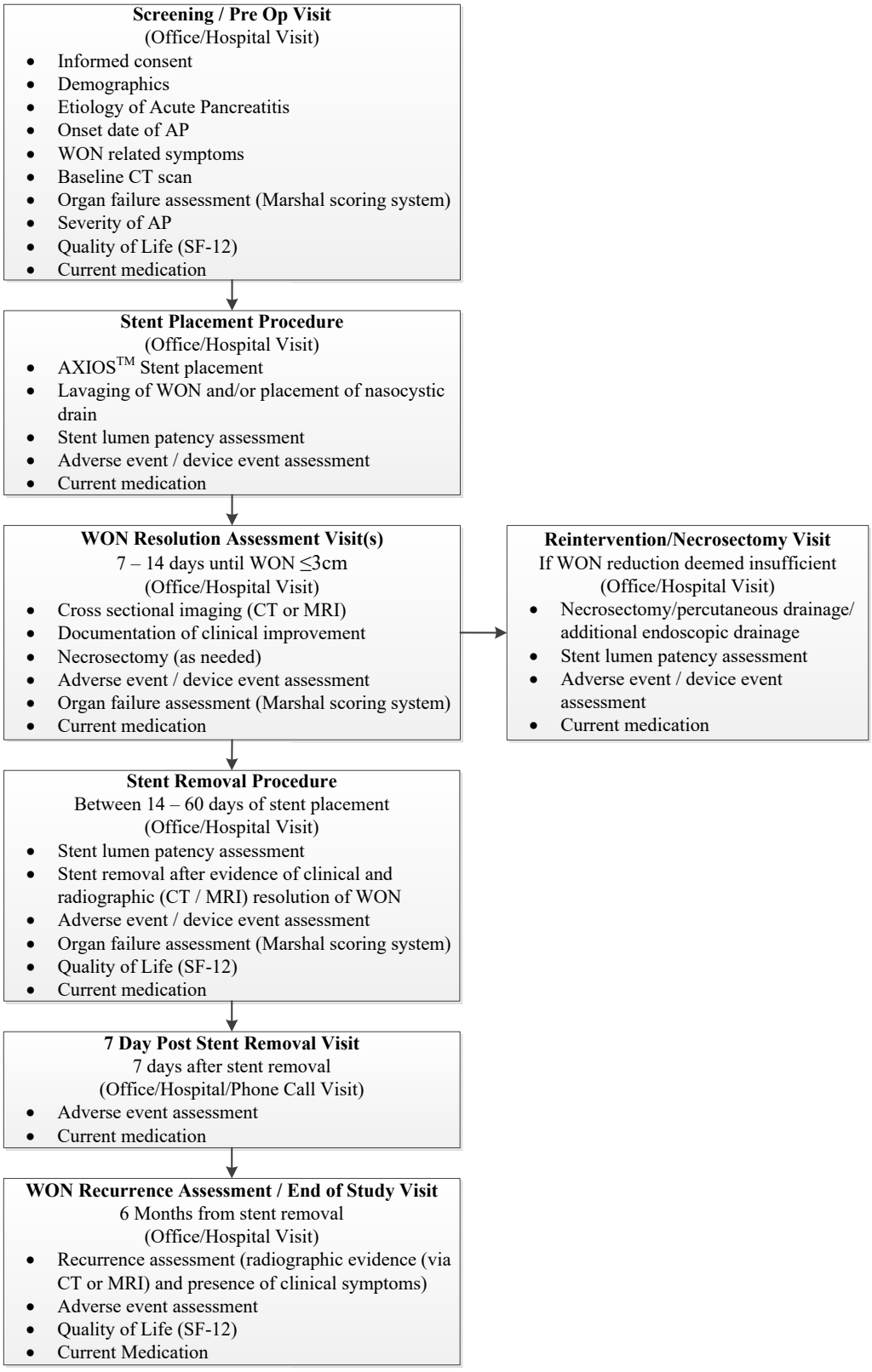
4.3 *Additional Endpoints*

1. Reduction of WON-related clinical symptoms.
   Note: WON-related symptoms as defined in Inclusion Criteria #4
2. Technical AXIOS™ stent placement success, defined as placement in desired location using endoscopic/EUS techniques per standard of practice.
3. Technical AXIOS™ stent removal success, defined as ability to remove the AXIOS™ stent using an endoscopic snare or forceps or graspers without AXIOS™ stent removal related serious adverse events.
4. Drainage procedural time: Time elapsed between initial puncture of the WON with electrocautery to endoscope retrieval.
5. Resolution of WON with or without necrosectomy by 6 months post AXIOS™ stent removal.
6. Time to WON resolution using same definition as for primary endpoint, namely:
   - Resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI.
7. Recurrence of WON after initial resolution and up to 6 months post AXIOS™ stent removal.
8. Stent lumen patency, evaluated via imaging or direct visual inspection with endoscope, and defined as one or both of the following:
   - Drainage through AXIOS™ stent visualized from the stomach or bowel, and/or
   - Visual confirmation of AXIOS™ stent lumen patency
9. Fluoroscopy (time) per endoscopic procedure.
10. Incidence of new organ failure from drainage procedure to WON resolution.
11. Change in Quality of life score (SF-12 questionnaire) from baseline to stent removal and end of study

4.4 *Study Design*

This study is a prospective, multi-center, single arm, consecutive series study. Treatment of up to 40 subjects will take place at up to 6 clinical centers. Subjects who meet all eligibility criteria will receive the AXIOS™ stent for up to 60 days stent indwell and 6 months follow-up after stent removal.

Figure 4.4-1: WON Drainage IDE Study Design



5 Subject Selection

5.1 *Inclusion Criteria*

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criteria is met.

1. Age between 22 and 75 years old
2. Severe or moderately severe acute necrotizing pancreatitis, defined per the 2012 Revised Atlanta Classification[1]
3. WON resulting from necrotizing pancreatitis per contrast-enhanced CT with the following characteristics, per the 2012 Revised Atlanta Classification: [1]

   • Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous)

   • Well defined wall

   • Location-intrapancreatic and/or extrapancreatic
4. Infected WON or symptomatic sterile WON

   Note: WON-related symptoms may include: pain, fever, leukocytosis, failure to thrive or deterioration of overall heath score, gastric outlet obstruction (GOO), weight loss, biliary obstructive symptoms, systemic inflammatory response syndrome (SIRS), deteriorating organ function, chronic nausea, lethargy, and inability to eat or gain weight
5. Imaging suggestive of greater than 30% necrotic material
6. WON ≥ 6cm in size
7. Eligible for endoscopic intervention
8. Acceptable candidate for endoscopic transluminal drainage
9. Patient understands the study requirements and the treatment procedures and provides written Informed Consent
10. Patient is willing to comply with all specified follow-up evaluations, including willingness to undergo a pre/post CT imaging study

5.2 *Exclusion Criteria*

Subjects who meet any one of the following criteria will be excluded from this clinical study.

1. Pseudocyst
2. Cystic neoplasm
3. Untreated Pseudoaneurysm > 1cm within the WON
4. More than one WON clearly separated and requiring drainage

5. WONs that require dual modality interventions (endoscopic and percutaneous) from the beginning (i.e. deep paracolic space involvement that is inaccessible through the central drainage access)
6. Prior surgical, interventional radiology or endoscopic procedures for the treatment of the WON
7. Abnormal coagulation:
    - INR > 1.5 and not correctable
    - presence of a bleeding disorder
    - platelets < 50,000/mm^3
8. Intervening gastric varices or unavoidable blood vessels within the access tract (visible using endoscopy or endoscopic ultrasound)
9. WON that poorly approximates the GI lumen (≥1cm away)
10. Pericolic gutter necrosis
11. Pelvic necrosis
12. Prior true anaphylactic reaction to contrast agents, nitinol (nickel titanium), silicone or any other materials contacting the patient
13. Female of childbearing potential with a positive pregnancy test prior to the procedure or intends to become pregnant during the study
14. Currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study

5.3 *Point of Enrollment*

A subject is considered "enrolled" after signing the study-specific Informed Consent Form (ICF). Subjects who sign the ICF but subsequently do not meet one or more of the selection criteria will be considered screen failures and excluded from the study.

5.4 *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal include physician discretion, subject choice to withdraw consent, loss to follow-up and death. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable case report forms up to the point of subject withdrawal must be completed. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open

adverse events should be closed or include resolution status. Data collected up to the point of subject withdrawal may be used. Withdrawn subjects will not be replaced. Subjects who withdraw from the study with the study stent in place will be followed per standard of care at the local institution.

5.5 *Subject Status and Classification*

Enrolled Cohort

A subject will be considered enrolled when the ICF is signed.

Intent-to-treat Cohort

The intent-to-treat (ITT) cohort is defined as all subjects who signed the ICF, were evaluated for inclusion/exclusion criteria, and in whom the endoscopic procedure was initiated.

Treated Cohort

The treated cohort is defined as all ITT subjects who have an AXIOS™ stent implanted for the purpose of WON drainage. Subjects in the trated cohort will be counted towards the enrollment ceiling and this cohort will be considered the primary analysis cohort.

Per Protocol Cohort

The per-protocol cohort is defined as all treated subjects for whom an AXIOS™ stent was implanted for the purpose of WON drainage and met all eligibility criteria.

5.6 *End of Study Action Plan*

Subjects will have the study test device, the AXIOS™ Stent, implanted temporarily for up to 60 days. A subject will be considered lost to follow-up if the subject remains unresponsive to communication after three documented attempts by study staff. However, for those subjects who remain unresponsive to communication while the stent remains in place, additional attempts will be made to request the subject's return for study stent removal. These additional attempts may include increased telephone and written communications and contact with the subject's primary care physician (if this communication is consented to in the Informed Consent Form).

6 Study Methods

6.1 *Data Collection*

Procedure/ Assessment	**Screening/ Pre-Op Visit**	**Stent Placement Procedure**	**WON Resolution Assessment Visit** (7 (+/- 3 days) /14 (+/- 5 days) for inpatients/outpatients)	**Reintervention / Necrosectomy Visit** (when needed)	**Stent Removal Visit** (14 -60 days from stent placement)	**7 Day Post Stent Removal Visit** (+/- 3 days)	**WON Recurrence Assessment Visit/End of Study** (6 months (+/- 14 days) from stent removal)
Informed Consent	X						
Eligibility Criteria	X						
Demographics	X						
Etiology of AP	X						
Onset of AP	X						
Severity of AP	X						
WON related symptoms	X		X				X
Imaging^{+++}	X^{+}		X	X**			X**
Organ Failure	X		X		X		
Quality of Life (SF-12)	X*				X		X
Laboratory Tests	X	X^{++}	X**	X**			X**
Current Medication	X	X***	X***	X***	X***	X***	X***
Stent Placement		X					
Lavaging of WON and/or placement of Nasocystic Drain		X**					
Stent Lumen Patency		X		X	X		
Necrosectomy				X**			
Percutaneous or Additional Endoscopic Drainage				X**	X**		
Stent Removal					X		
Adverse Event Assessment		X	X	X	X	X	X
Device Event Assessment		X	X	X	X		

X = Required
* = If the SF-12 is not done due to the condition of the patient, this will not be considered a protocol deviation

** = As needed per standard of care
*** = Documentation of any changes in medication since previous visit
+ = Imaging should be done within 2 weeks of the initial drainage procedure
++ = Labs need to be repeated at this visit ONLY IF they were colletect more than 3 days before the stent placement procedure.
+++ = Imaging may include CT with contrast (unless contraindicated), MRI, EUS

Study Candidate Screening

No study-specific testing will be conducted until after the subject has signed an ICF. A Screen Failure/Enrolled Log will be maintained in the Electronic Data Capture (EDC) system by the center to document select information about candidates who signed consent.

6.2 *Informed Consent*

Written Informed Consent must be obtained for all subjects who are potential study candidates. Subjects will be asked to sign the ICF before any study-specific tests or procedures are performed. The ICF is study-specific and must be approved by the study IRB/EC and Competent Authority (CA), as applicable. Study personnel should explain that even if a subject agrees to participate in the study and signs the ICF, the EUS procedure may demonstrate that the subject is not a suitable candidate for the study.

6.3 *Visit Schedule*

Screening / Pre-op Visit – Office/Hospital Visit:

- Informed Consent
- Demographics
- Etiology of AP
- Onset date of AP
- WON related symptoms
- CT Scan or MRI (identification of percentage of necrosis and confirmation of absence of pseudoaneurysms inside WON)
- Organ failure assessment (Marshal scoring system)
- Severity of AP
- Labs
- Quality of Life (SF-12)
  Note: If the SF-12 is not done due to the condition of the patient, this will not be considered a protocol deviation
- Current medication

Stent Placement Procedure – Office/Hospital Visit

- AXIOS™ stent placement
  Note: Physicians will select the site of the AXIOS™ stent placement under endoscopic guidance and choose an access location that is free from necrotic debris and intervening blood vessels, where the wall between the GI tract and fluid collection is 10mm or less,

and where it is possible to place the AXIOS™ stent in a position such that the inner flange (inside WON) has enough space to expand.

- Lavaging of WON under endoscopic visualization and/or placement of nasocystic drain, or a single, 7fr double pigtail plastic stent (Boston Scientific 7Fr Advanix™ Biliary Stent) through the AXIOS™ stent at the discretion of investigator
- Stent lumen patency assessment
- Adverse event assessment/device event assessment
- Current medication
- Labs (as needed)
  Note: Labs need to be repeated at this visit ONLY IF they were collected more than 3 days before the stent placement procedure.

Multiple Interventions During Index Procedure:
Once stent is placed into the WON, dilation of the AXIOS™ stent is allowed to expand the stent if needed. Dilation can be performed to the maximal diameter of the AXIOS™ stent. A single, 7 fr double pigtail plastic stent (Boston Scientific 7Fr Advanix™ Biliary Stent) may be placed through the AXIOS™ stent at the discretion of the investigator. Access to the WON with a forward viewing diagnostic or therapeutic upper gastroscope is allowed up to 20 minutes (from time of endoscopic access of the WON) to break-up large chunks of necrosis and lavage collection at the discrection of the physician.

<u>WON Resolution Assessment - 7 days (+/- 3 days) for inpatients and 14 (+/- 5 days) days for outpatients (needed until radiographic decrease of WON size to ≤ 3cm) – Office/Hospital Visit:</u>

- Cross sectional imaging (CT or MRI) to assess reduction in WON size. If reduction in size is deemed insufficient, necrosectomy will be initiated
- Documentation of clinical improvement defined as improvement of principal WON-related symptoms
- Necrosectomy (as needed)
- Adverse event assessment/device event assessment
- Organ failure assessment (Marshal scoring system)
- Current medication
- Labs (as needed)

<u>Reintervention/Necrosectomy Visits when needed during AXIOS™ stent indwell – Office/Hospital Visit:</u>

- Necrosectomy initiated if WON reduction in size is deemed insufficient during WON Resolution Assessment Visit. Duration of each necrosectomy session is limited to 60 minutes
- Percutaneous drainage or additional endoscopic drainage may be needed if reduction in WON size is insufficient or in cases of continued WON related symptoms such as infection/sepsis despite necrosectomy. Choice of stent (AXIOS™ or plastic double pigtail

stent(s)) for repeat endoscopic drainage procedures will be left to the discretion of the investigator. The double pigtail plastic stent(s) or new AXIOS™ stent may be placed through the tract established by the original AXIOS™ stent or in a separate location.
- Stent lumen patency assessment
- Imaging (as applicable)
- Labs (as needed)
- Adverse event assessment/device event assessment
- Current medication

Stent Removal Visit - between 14 days and 60 days (+/- 7 days) of stent placement – Office/Hospital Visit

- Stent lumen patency assessment
- Stent removal after evidence of clinical and radiographic (via CT or MRI) resolution of WON
  Note: Removal of stent by 60 days is required if WON not resolved. Patients with unsuccessful or incomplete WON resolution by 60 days will proceed to standard of care treatment outside of this protocol after removal of the AXIOS™ stent; however, the patient outcome will continue to be followed. Alternative interventions may include surgery, endoscopic drainage with double pigtail plastic stents, percutaneous catheter drainage and necrosectomy (video-assisted retroperitoneal debridement (VARD), or endoscopic transluminal debridement, or open necrosectomy).
- Adverse event assessment/device event assessment
- Organ failure assessment (Marshal scoring system)
- Quality of Life (SF-12)
- Current medication

7 Day (+/-3 days) Post Stent Removal Visit – (Office or phone call):

- Adverse Event assessment
- Current medication

WON Recurrence Assessment Visit/End of Study – at 6 Months (+/- 14 days) from stent removal:
- Recurrence assessment (presence of clinical symptoms and further diagnosis per standard of care (e.g. labs and imaging)
- Adverse Events assessment
- Quality of Life (SF-12)
- Current medication

6.4 *Study Completion*

Subjects will be followed for 6 months after stent removal.

Additional visits may be conducted at the Investigator's discretion in accordance with Adverse Event or Device Event data collection. A subject will be considered lost to follow-up if the subject remains unresponsive to communication after three documented attempts by study staff.

6.5 *Source Documents*

The Investigator/institution guarantees direct access to original source documents, including imaging documentation, by BSC personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review.

7 Statistical Considerations

7.1 *Effectiveness Endpoint*

Primary Effectiveness Endpoint:

The primary effectiveness endpoint for this study is the resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI

Primary Effectiveness Endpoint Assessment:

Note: Success will be based on the number of WONs resolved, not on the number of AXIOS™ Stents required to achieve resolution.

- If it is determined that the fluid collection is actually two separate collections, and each collection is drained via an AXIOS™ stent, then each collection will be assessed individually via the drainage success criteria of ≤3cm.
- If it is determined that the fluid collection is a single collection but the drainage is inadequate via a single AXIOS™ stent, then the success of the AXIOS™ drainage will be assessed as follows:
    - If a second AXIOS™ stent is used at a new drainage site/original drainage site and the entire fluid collection is drained to meet the success criteria of ≤3cm then the collection will be considered to be a single collection drainage success.
    - If a second AXIOS™ stent is used at a new drainage site and the entire fluid collection does not drain adequately to meet the drainage success criteria of ≤3cm then the fluid drainage of the collection will be considered to be a single drainage failure.
    - If a plastic stent is used at a new drainage site and the entire fluid collection drains to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered indeterminate.

- If a single, 7fr plastic stent is used at the same drainage site, through the AXIOS™ stent, and the entire fluid collection drains to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered a single collection drainage success.
- If a plastic stent is used at a new drainage site and the entire fluid collection does not drain to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered a single drainage failure.

Hypothesis:

As in the original IDE, #G130264, there is no formal statistical hypothesis for this study. The proportion of AXIOS patients with reduction of WON size to ≤ 3cm within 60 days from AXIOS™ stent placement in the original IDE is 76.7% (23/30) [95% CI (57.7%, 90.0%)] patients. Given that the WONs in the proposed IDE will have an estimated necrotic material content above 30%, namely larger than in IDE #G130264, a slightly lower success rate of 70% is expected in this study. This success rate is within the range of reported WON resolution rates in several recent publications [2-8] representing 448 patients for which a random effects meta-analysis yields a mid-point WON resolution rate of 67.0% [95% CI (60.0%, 73.4%)] for WON drainage with plastic stents (Table 7.1), an established WON drainage method as described in the ASGE guidelines on treatment of pancreatic fluid collections [9].

Table 7.1 Plastic Stent WON Resolution Rates from Recent Publications

Study	% Resolution (x/N)	95% Confidence Interval
Bapaye (2017)	73.8% (45/61)	(60.9%, 84.2%)
Gardner et al (2009)	68.9% (31/45)	(53.4%, 81.8%)
Papachristou (2007)	52.8% (28/53)	(38.6%, 66.7%)
Schmidt (2015)	61.7% (50/81)	(50.3%, 72.3%)
Smoczynski (2015)	75.9% (85/112)	(66.9%, 83.5%)
Abu Dayyeh (2017)	75.0% (27/36)	(57.8%, 87.9%)
Varadarajulu (2011)	60.0% (36/60)	(46.5%, 72.4%)
Random-Effects Meta-Analysis	**67.0%**	**(60.0%, 73.4%)**

Statistical Methods:

The primary effectiveness endpoint will be summarized as the proportion of patients who have resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI out of all patients who have an AXIOS™ stent successfully implanted. A Clopper-Pearson exact 95% confidence interval will also be calculated.

7.2 *Safety Endpoint*

Primary Safety Endpoint:

The Primary Safety Endpoint is AXIOS™ stent related or WON drainage procedure related serious adverse events.

Primary Safety Endpoint Assessment:

If it is determined that the patient has an infection, then the primary safety success of the AXIOS™ device or the drainage procedure will be assessed as follows:

- If the patient presents with an infected collection at the initial drainage procedure, the infection will be classified as a localized infection and will not be considered a stent related or WON drainage related serious adverse event
- If the patient presents with a sterile collection at the initial drainage procedure and post-procedurally develops an infected collection, the infection will be classified as a localized infection and will not be considered a stent related or WON drainage related serious adverse event as this is a known consequence of any endoscopic drainage procedure, where the access route to the collection is through a non-sterile GI lumen and is not a function of a particular stent or device

  (*Note: If the stent is occluded at the onset of infection, then the infection will be attributed to the device. If the stent remains unobstructed at the time of infection, then the infection will not be attributed to the device.)*
- If the patient presents with a sterile collection at the initial drainage procedure and then post-procedurally develops a wide-spread infection in the form of sepsis or blood stream infection, then the infection will be classified as systemic and will be considered a stent related or WON drainage related serious adverse event only if the AXIOS stent was clearly and visually occluded by solid necrosis at the time of repeat endoscopy. This determination will be made by the operating physician at the time of endoscopy

Hypothesis:

As in the original IDE, #G130264, there is no formal statistical hypothesis for this study. The proportion of AXIOS patients with AXIOS™ stent related or WON drainage procedure related serious adverse events in the original IDE is 10.0% (3/30) [95% CI (2.1%, 26.5%)] patients. A similar rate of AXIOS™ stent related or WON drainage procedure related serious adverse events is expected in this study. This event rate is within the range of reported stent related or WON drainage procedure related serious adverse event rates in several recent publications [3-5, 10] representing 306 patients for which a random effects meta-analysis yields a mid-point related SAE rate of 16.7% [95% CI (10.1%, 26.3%)] for WON drainage with plastic stents (see Table 7.2 and Table 7.3 (categorized events from Table 7.2)), an established WON drainage method as described in the ASGE guidelines on treatment of pancreatic fluid collections [9].

Table 7.2 Plastic Stent-related or WON Drainage-procedure related Serious Adverse Events Rates from Recent Publications [3-5, 10]

Study	% Related SAEs (x/N)	95% Confidence Interval
Papachristou (2007)	20.8% (11/53)	(10.8%, 34.1%)
Schmidt (2015)	12.3% (10/81)	(6.1%, 21.5%)
Smoczynski (2015)	25.9% (29/112)	(18.1%, 35.0%)
Varadarajulu (2011)	8.3% (5/60)	(2.8%, 18.4%)
Random-Effect Meta-Analysis	**16.7%**	**(10.1%, 26.3%)**

Table 7.3 Categorized Plastic Stent-related or WON Drainage-procedure related Serious Adverse Events Rates from Recent Publications [3-5, 10]

SAE	% (x/N)
Bleeding	11.1% (34/306)
Perforation	2.6% (8/306) [5 GI; 2 Collections; 1 Undefined]
Pneumoperitoneum	1.3% (4/306)
Sepsis	0.7% (2/306)*
Stent migration	1.0% (3/306)
Multiple organ failure	1.0% (3/306)
Other - loss of access to the collection (due to hypertension)	0.3% (1/306)

*Note: 1 patient with septic shock also had multiple organ failure (death)

Statistical Methods:

The primary safety endpoint will be summarized as the proportion of patients who have AXIOS™ stent related or WON drainage procedure related serious adverse events out of all patients who have an AXIOS stent successfully implanted. A Clopper-Pearson exact 95% confidence interval will also be calculated.

7.3 *Sample Size and Success Criteria*

The WON resolution rates and related SAE rates reported in the above provided study references are similar to those reported for WON drainage using plastic stents in a recent systematic review and meta-analysis comparing plastic stents to metal stents, including lumen-apposing metal stents (LAMS) for the management of WONs [28]. Appendix I in Section 21 provides a few key points from this systematic review.

Although reported effectiveness and safety event rates from different sources appear similar, 95% confidence intervals are fairly wide, mostly due to small sample sizes and heterogeneity in WONs and in detailed procedural WON drainage steps. Therefore we chose to increase the sample size of the present study to be slightly larger than in the original IDE study #G130264, which was 30 patients.

We will conduct the present study in 40 patients.

Effectiveness Endpoint Success Criteria

An observed rate of 67% or higher for the proportion of AXIOS patients with reduction of WON size to ≤ 3cm within 60 days from AXIOS™ stent placement is required for success.

This rate is the same as the point estimate of the random-effect meta-analysis of WON resolution rates provided in Table 7.1. Note that in the recent systematic review and meta-analysis [28] (Appendix I in Section 21) WON resolution rates were higher and number of procedures required to reach WON resolution were lower when using LAMS compared to plastic stents for WON drainage. Thus the proposed success criteria for effectiveness seems reasonable.

Safety Endpoint Success Criteria

An observed rate of 17.5% or lower for the proportion of AXIOS patients with AXIOS™ stent related or WON drainage procedure related serious adverse events is required for success.

This rate is similar to the point estimate of the random-effect meta-analysis of AXIOS stent related or WON drainage related serious adverse events provided in Table 7.2. Note that in the recent systematic review and meta-analysis [28] (Appendix I in Section 21) the complication rates that showed statistically significant differences between plastic stents and LAMS for drainage of WONs were bleeding and stent occlusion, both in favor of LAMS. These findings are particularly important given that (a) bleeding is the most commonly reported serious adverse event, and (b) stent occlusion almost always requires reintervention. It should also be noted that of the plastic stent WON drainage references provided above, even the one reporting the highest complication rates, namely Smoczynski et al [5] conclude that the benefits outweigh the risks: "*In a large group of selected patients with symptomatic walled-off necrosis, endoscopic drainage enables high success rate with acceptable complication rate and low procedure-related mortality*." Thus the proposed success criteria for safety seems reasonable and acceptable.

7.4 *General Statistical Methods*

Control of Systematic Error/Bias:

All subjects who have met the inclusion/exclusion criteria and have signed the ICF will be eligible for enrollment in the study. Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

Number of Subjects per Investigative Site:

There will be no limit to the number of subjects enrolled at each investigative site.

Data Analysis:

Descriptive statistics will be presented for all ITT and treated subjects. If the treated and PP cohorts are different, the primary effectiveness and safety endpoints will be assessed for the PP cohort. The mean, standard deviation, minimum, and maximum will be used to describe continuous variables; the median (and interquartile range) will be calculated where appropriate. Frequency tables will be used to summarize discrete variables. Proportions of subjects with adverse events and SAEs will be reported.

Interim Analysis:

No formal interim analyses are planned for the purpose of stopping this study early. Informal interim analysis may be conducted for the purpose of submissions of abstracts to major professional meetings.

Subgroup Analysis:

There are no planned subgroup analyses.

Justification of Pooling:

The analyses will be performed using data pooled across institutions and whether patients had a double pigtail plastic stent placed within the Axios stent. An assessment of the poolability of subjects across sites (double pigtail plastic stent groups) for the primary effectiveness and safety endpoints will be made by fitting logistic regression models with site (double pigtail plastic stent) as a factor and the primary effectiveness and safety endpoints as outcomes. Certain baseline variables may also be explored for pooling.

If the P value for the site (double pigtail plastic stent) is ≥ 0.05, it will be concluded that the endpoint is not different across sites (double pigtail plastic stent groups), and the data can be pooled. If the P value for site (double pigtail plastic stent) from the logistic model is <0.05, site (double pigtail plastic stent group) differences will be explored.

Multivariable Analyses:

No multivariable analyses are planned for this study.

Changes to Planned Analyses:

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

8 Data Management

8.1 *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure EDC system. The clinical database will reside on a production server hosted by EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its

representatives. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly. The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs). A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes. Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

8.2 *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations.

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

9 Amendments

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

10 Deviations

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

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

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

11 Device/Equipment Accountability

The investigational devices shall be securely maintained, controlled, and used only in this clinical study. Equipment shall be returned in the condition in which it was provided, reasonable wear and tear excepted.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices from BSC equipment to the investigation sites until return or disposal.

Records shall be kept by study personnel to document the physical location and conditions of storage of all investigational devices.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following:

- Date of receipt
- Identification of each investigational device (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

Written procedures may be required by national regulations.

12 Compliance

12.1 *Statement of Compliance*

This study will be conducted in accordance with relevant sections of the International Standard (ISO) 14155: Clinical Investigation of Medical devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable

opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

12.2 *Investigator Responsibilities*

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

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

- Prior to beginning the study, sign the Clinical Study agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to the beginning of the study, sign the Investigator Brochure Signature Page and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure, including stent removal and complete distal migration) every adverse event and observed device deficiency.
- Report to BSC per the protocol requirements and the IRB/EC, as applicable, all SAEs and device deficiencies that could have led to a Serious Adverse Device Event (SADE).
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.

- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

12.2.1 Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated, and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at at site, the sub investigator should not be delegated the primary supervisory repsonsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

12.3 *Institutional Review Board/ Ethics Committee*

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

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

Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC/REB requirements. Copies of the Investigator's reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

12.4 *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performace of its device, new medical research and proposals for develping new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third party researcher will be without identifiable reference to specific subject.

Information received during the study will not be used to market to subject; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

12.5 *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

13 Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

14 Potential Risks and Benefits

14.1 *Anticipated Adverse Device Effects*

Possible Adverse Events associated with the use of the AXIOS™ Stent and Electrocautery-Enhanced Delivery System may include those often associated with any endoscopic procedure. These complications include:

- Anesthesia complications
- Improper AXIOS Stent placement; incomplete deployment; stent migration into the fluid collection or, GI tract; separation of coating material from stent; stent fracture; coating material wear; coating material failure; puncture of coating material
- Tissue ingrowth or overgrowth leading to difficulty or a failure to remove stent
- Stent dislodgement
- Adverse reaction to implant materials and/or delivery system (e.g., abdominal or back pain, nausea, infection, fever, chronic inflammation or foreign body reaction)
- Minor or excessive bleeding requiring intervention
- Leakage of fluid collection or bowel contents causing inflammation or peritonitis
- Stent occlusion
- Local infection at the implant site
- Tissue damage during stent implantation and/or removal
- Ulceration or erosion of mucosal or organ wall linings
- Pneumoperitoneum
- Sepsis (bacterial, endotoxin or fungal)
- Perforation
- Surgical intervention (endoscopy, transfusion or surgery)
- Persistent connection to the fluid collection after removal (fistula)
- Unintended electrical shock, muscle stimulation or burns
- Cardiac arrhythmia or arrest
- Death

Please refer to the Investigator Brochure for a list of anticipated adverse device effects.

14.2 *Anticipated Benefits*

Subjects may not receive any benefit from participating in this study. However, medical science and future subjects may benefit from this study.

14.3 *Risk to Benefit Rationale*

Based on collected reports in literature to-date, the risk-to-benefit ratio is within reason for foreseeable risks. However, literature reports do not always capture all side effects. Observation and follow-up of subjects is required as outlined in the protocol.

15 Safety Reporting

15.1 *Reportable Events by Investigational Site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects*
- New findings/updates in relation to already reported events
- All Device Related Adverse Events
- All Study Procedure, Removal Procedure and Necrosectomy Procedure Related Adverse Events

* BSC Medical Safety will be responsible for all UADE assessments. Unanticipated means the effect, problem, or death is not previously identified in nature, severity, or degree of incidence in the investigational plan or application, investigator's brochure, DFU/IFU, informed consent or other risk documents.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 15.2-1 for AE definitions).

Refer to Section 14 for the known risks associated with the study device(s).

15.2 *Definitions and Classification*

Adverse event definitions are provided in Table 15.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 15.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, as defined by either: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Table 15.2-1: Safety Definitions

Term	Definition
Ref: ISO 14155 *Ref: MEDDEV 2.7/3*	
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	A device deficiency is any inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance.This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

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

15.3 *Relationship to Study Device(s)*

The Investigator must assess the relationship of any SAE or AE to the study device, study stent placement or removal procedure, and necrosectomy procedure. See criteria in Table 15.3-1:

Table 15.3-1: Criteria for Assessing Relationship of Study Device, Procedure, Stent Removal and any Complete Distal Migration to Adverse Event

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

Table 15.3-1: Criteria for Assessing Relationship of Study Device, Procedure, Stent Removal and any Complete Distal Migration to Adverse Event

Classification	Description
	o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

15.4 *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 15.4-1.

Table 15.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (Pre-Market Studies) (MEDDEV 2.7/3): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event upon request of the sponsor	• At request of sponsor
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event upon request of the sponsor	• At request of sponsor

Table 15.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (Pre-Market Studies) (MEDDEV 2.7/3): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event	• When documentation is available • At sponsor request
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event	• At request of sponsor
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required through end of study • At sponsor request
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event	

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

15.5 *Boston Scientific Device Deficiencies*

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

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

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

15.6 *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

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

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

16 Informed Consent

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

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

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

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

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

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

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

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

17 Suspension or Termination

17.1 *Premature Termination of the Study*

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

17.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

17.2 *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval*

Any investigator, or associated IRB/ EC/REB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

17.3 *Requirements for Documentation and Subject Follow-up*

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

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

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

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

17.4 *Criteria for Suspending/Terminating a Study Center*

Boston Scientific reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 12 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, should be notified. All subjects enrolled in the study at the center will continue to be followed for the protocol follow-up period after study termination. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

18 Publication Policy

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

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

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20 Abbreviations and Definitions

Acronym	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AP	Acute Pancreatitis
ASGE	American Society for Gastrointestinal Endoscopy
ASADE	Anticipated Serious Adverse Device Effect
BSC	Boston Scientific Corporation
CA	Competent Authority
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EUS	Endoscopic Ultrasound
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GOO	Gastric Outlet Obstruction
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-To-Treat
MRI	Magnetic Resonance Imaging
PFCs	Pancreatic Fluid Collections
PP	Per Protocol
SF12	Short Form 12-item Survey
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SIRS	Systemic Inflammatory Response Syndrome
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

VARD	Video-Assisted Retroperitoneal Debridement
WON	Walled-off Pancreatic Necrosis

21 Appendix A. Key points extracted from Bazerbachi et al (GIE 2017) [28]

The WON drainage stent types for cases represented in the Bazerbachi et al (GIE 2017)[28] systematic review and meta-analysis included 2213 patients

- 1202 patients with WON drainage using plastic stents
- 1011 patients with WON drainage using metal stents
    - 871 patients with WON drainage using Lumen Apposing Metal Stents (LAMS)
        - 503 patients with WON drainage using AXIOS LAMS
        - 368 patients with WON drainage using non-AXIOS LAMS
    - 140 patients with WON drainage using non-LAMS

Table A1. Summary of Meta-Analysis Metrics Results

Metric	Plastic stents	Metal stents	Lumen-apposing metal stents
Two arm-studies			
Overall resolution	80.9%	92.1% (OR: 2.8; 95% CI, 1.7-4.6; $P < .001$)	91.5% (OR, 2.5; 95% CI, 1.4-4.3; $P = .001$)
Rate of resolution with a single procedure	43.4%	47.1% (OR: 1.3; 95% CI, 0.7-2.4; $P = .2$)	52.3% (OR, 1.4; 95% CI, 0.56-3.6; $P = .4$)
Number of procedures to achieve resolution	Mean difference −.92 (95% CI, −1.283-.561, $p < 0.001$) (favoring metal stents)		
Bleeding	7.1%	3.6% (OR: 0.5; 95% CI, 0.15-1.7; $P = .2$)	5% (OR, 0.64; 95% CI, 0.13-3.1; $P = .5$)
Perforation	3%	1.9% (OR: 0.6; 95% CI, 0.15-2.7; $P = .5$)	4% (OR, 1.2; 95% CI, 0.24-6.18; $P = .8$)
Stent migration	5.3%	6.7% (OR: 1.3; 95% CI, 0.6-2.6; $P = .4$)	6.3% (OR, 1.12; 95% CI, 0.51-2.47; $P = .7$)
Stent occlusion	16.9%	11.7% (OR: 0.6; 95% CI, 0.34-1.1; $P = .1$)	3.8%(OR, 0.36; 95% CI, 0.03-4; $P = .4$)
One-arm studies			
Bleeding	12.6% [95% CI, 9.5%-16.5%]	5.6% [95% CI, 3.6%-8.6%] ($P = .002$)	6.2% [95% CI, 3.9%-9.6%] ($P = .007$)
Perforation	4.3% [95% CI, 3.1%-6%]	2.8% [95% CI, 1.6%-5%] ($P = .2$)	3.8% [95% CI, 2.1%-6.9%] ($P = .7$)
Stent migration	5.1% [95% CI, 2.6%-10.1%]	8.1% [95% CI, 5.1%-12.6%] ($P = .2$)	7.8% [95% CI, 4.7%-12.5%] ($P = .3$)
Stent occlusion	17.4% [95% CI, 9.4%-29.9%]	9.5% [95% CI, 7.5%-12.1%] ($P = .07$)	7.5% [95% CI, 5.6%-9.9%] ($P = .015$)

22 Appendix B. S-F12

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

1. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

2. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

1. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical</u>**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

<u>health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

Thank you for completing these questions!