AXIOS™ for Gallbladder Drainage as an Alternative to Percutaneous Drainage IDE

NCT03767881

Clinical Protocol

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A Multicenter, Prospective Study of EUS-Guided Transluminal Gallbladder Drainage in Patients with Acute Cholecystitis as an Alternative to Percutaneous Gallbladder Drainage

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Clinical Investigation Plan

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
92147168, Rev/Ver B	December 20, 2017	Template 90702637 Rev/Ver AH	Synopsis, 2, 3, 4, 5, 6, 7, 8, 15, 16, 17	Wording modifications including: Study title, device description, study objective, endpoints, inclusion criterion, exclusion criterion, subject status and classification, additional procedural notices, study methods, statistical considerations and general statistical methods, committees, risk management strategy, and safety reporting	Per FDA review and feedback
92147168, Rev/Ver C	May 17, 2018	Template 90702637 Rev/Ver AH	Study Objective, Synopsis, Exclusion Criteria 5, 6, 7, 8, 16, 5.2	Added statement to Study Objective, Changed Exclusion Criteria # 9; add collection of current medications at baseline and follow-up visits and exclude patients with any prior interventions; change follow-up of patients who do not have an AXIOS stent implanted; change primary analysis cohort and enrollment cohort to ITT; specify the evaluation of the primary effectiveness endpoint; minor edits to section 7.4 to match synopsis; added exclusion criterion. Added windows for end of study visit and 72hr post stent removal visit; raised the number of participating centers	Per FDA review and feedback
92147168, Rev/Ver D	August 15, 2018	Template 90702637 Rev/Ver AJ	Synopsis, Section 7, 17, 18, 20, 21	Updated language to reflect updated protocol template	Updated protocol template

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
92147168, Rev/Ver E	September 05, 2018	Template 90702637 Rev/Ver AJ	Synopsis, Section 5.1, Figure 4.3-1, 8.1	Updated inclusion criteria #2 in Synopsis and Section 5.1; updated flowchart in Figure 4.3-1; added that patient not receiving an Axios stent will be censored in the KM analysis at 60 days. Added a sensitivity analysis for the KM analysis; updated number of centers in synopsis	Per FDA review and feedback
92147168, Rev/Ver F	October 18, 2018	Template 90702637 Rev/Ver AJ	Synopsis, Section 4.1; Contact information	Updated primary effectiveness endpoint in synopsis and section 8.1; Changed sample size to 24 patients; Updated coordinating lead investigator	Per FDA review and feedback
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92147168, Rev/Ver I	February 20, 2020	Template 90702637 Rev/Ver AL	Synopsis, section 5.2, section 4.4, section 6.5, section 7.4	Updated exclusion criteria #5 in synopsis and section 5.2, increased number of centers in section 4.4; study design, added definition of end of study in section 6.5 end of study, moved clinical symptom assessment to stent removal visit in section 7.4	Updated protocol template; improve study enrollment
92147168, Rev/Ver J	June 06, 2020	Template 90702637 Rev/Ver AL	Synopsis, section 5.2, section 7.4	Updated exclusion criteria #9 in synopsis and section 5.2, updated imaging window flowchart; added repeat imaging procedure in case of patient's deteriorating clinical status in section 7.4	Per FDA feedback

Protocol Synopsis

Full Title	**A Multicenter, Prospective Study of EUS-Guided Transluminal Gallbladder Drainage in Patients with Acute Cholecystitis as an Alternative to Percutaneous Gallbladder Drainage**
Short Title	AXIOS™ for Gallbladder Drainage as an Alternative to Percutaneous Drainage IDE
Background	The established treatment for acute cholecystitis in patients who are unsuitable or at high risk for surgery is percutaneous transhepatic gallbladder drainage (PT-GBD) also known as percutaneous cholecystostomy (PC). However, external drainage provided by percutaneous tubes is associated with high rate of complications, including peritonitis, bleeding, pneumothorax, recurrent cholecystitis, and secondary infections. In addition, percutaneous cholecystostomy tubes can be uncomfortable, have a negative effect on the patient's quality of life, [1] and may result in inadvertent dislodgement or intentional removal requiring numerous reinterventions. An alternative to PT-GBD is Endoscopic Ultrasound-guided Transmural Gallbladder Drainage (EUS-GBD) which is an internal drainage method having the potential to eliminate many of the shortcomings of PT-GBD [2]. The literature contains clinical results of the successful use of the AXIOS™ stent in EUS-GBD. The AXIOS™ transluminal stent system can be used to bridge two lumens or organs to create an internal drain. It is cleared in the U.S. to drain pancreatic pseudocysts into the stomach or the duodenum while outside the U.S. its indication includes EUS-GBD. The purpose of this IDE clinical trial is to evaluate the use of the AXIOS™ stent in the EUS-GBD procedure for gallbladder drainage into the stomach or duodenum.
Study Objective	To evaluate the safety and effectiveness of the AXIOS™ Stent with Electrocautery Enhanced Delivery System in the management of symptoms of acute cholecystitis as an alternative to percutaneous gallbladder drainage. It is anticipated that a transluminal EUS drainage approach with the AXIOS™ stent will provided benefits in time to resolution of acute cholecystitis as well as a lower the fraction of patients whom would require additional interventions compared to those treated with percutaneous cholecystostomy; study endpoints will be used to further evaluate.

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. 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 are 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 in the U.S. for this IDE study: The AXIOS™ Stent and Electrocautery Enhanced Delivery System is intended for endoscopic ultrasound-guided transluminal gallbladder drainage in patients with acute cholecystitis who are at high risk or unsuitable for surgery.
Test Device	AXIOS™ Stent and Electrocautery Enhanced Delivery System
Test Device Sizes	• Diameter: 10 mm, 15 mm • Length: 10mm
Study Design	Prospective, multi-center, single arm, consecutive series study
Number of Subjects	30 subjects
Number of Centers	Up to 9 sites (US and OUS)
Primary Effectiveness Endpoint	Time to resolution of acute cholecystitis measured in days. *Note:* Resolution is defined as either a fever of less than 100.5°F, or at least a 4-point decrease in the pain score, or WBC count less than 12,000/cc, with improvement in at least two of these categories without the deterioration of the third category.
Secondary Effectiveness Endpoint	Rate of re-interventions including but not limited to stent migration, stent occlusion by GB stones, and luminal debridement
Additional Endpoints	1. Stent patency (ability to facilitate gallbladder drainage) defined indirectly as resolution of acute cholecystitis or, in the absence of

	resolution of acute cholecystitis, endoscopic observation of unobstructed AXIOS™ stent lumen 2. Technical stent placement success: Successful stent placement, defined as transmural placement of the AXIOS™ stent with confirmed stent patency via (i) drainage visualized through the stent or fluoroscopically, or (ii) ability to endoscopically observe the inner walls of the gallbladder through the AXIOS™ stent 3. Technical stent removal success: Successful stent removal, defined as ability to remove the AXIOS™ stent endoscopically without stent removal related serious adverse events 4. Rate of recurrence of acute cholecystitis and its management 5. Number of cumulative hospital and ICU days from initial stent placement to resolution of symptoms of acute cholecystitis
Method of Assigning Subjects to Treatment	All subjects with acute cholecystitis at high risk or unsuitable for cholecystectomy and indicated for gallbladder drainage will be approached for participation.
Study Visits and Follow-Up Schedule	• **Screening/ Baseline Visit** (Office/Hospital Visit): informed consent, eligibility criteria assessment, pre-procedure transabdominal ultrasound or CT scan (within 5 days of drainage procedure), demographics, medical history, pre-procedural patient management including labs and clinical symptom assessment, laboratory markers of inflammation or cholestasis (including WBC), current medication(s) • **Stent Placement Procedure** (Office/Hospital Visit): stent placement procedure per DFU/ IB, adverse event/device event assessment, stent patency assessment, current medication(s) ***Additional Procedural Notices:*** o *Procedure should be done with CO_2 insufflation.* o *Choice of placement of stent between the duodenum and the gallbladder or between the stomach and the gallbladder is left at discretion of treating physician.* o *Physicians will select the site of the AXIOS stent placement under EUS guidance and choose an access location where there is* o *adequate stone-free space within the gallbladder to deploy the flange* o *distance between the gallbladder and the stomach or duodenal lumen that does not exceed 10mm, the saddle length of the AXIOS™ stent*

	○ *no intervening ascites, bowel, or fat, as identified by EUS* ○ *If a patient's gallbladder has minimal stone burden and is free of large stones per baseline imaging, a 10mm lumen diameter AXIOS™ stent is recommended* ○ *If a patient's gallbladder is packed with stones or large stones (1cm or larger in diameter) are present per baseline imaging, a 15mm lumen diameter AXIOS™ stent is recommended* ○ *Stones and/or sludge will be cleared using gentle basketing and irrigation through the stent if necessary, at the discretion of investigator* ○ *Placement of double pigtail plastic stent(s) through AXIOS™ will not be allowed in the study.* ○ *If placement of the AXIOS™ stent is attempted but no stent placement occurs, patient will be followed until 30 days after resolution of the cholecystitis, or 60 days after the index procedure, whichever comes first. The patient's treatment will be at the discretion of the physician.* • **Daily Acute Cholecystitis Assessment Visits** (Office/Hospital Visit): until discharge/resolution: clinical symptom assessment (including pain score, and fever), laboratory markers of inflammation, or cholestasis (including WBC), imaging (as applicable), adverse event / device event assessment, documentation of any re-intervention, including luminal debridement (as applicable), current medication(s) ○ *If discharged less than 72 hours post stent placement, patient may have a follow-up phone call instead: clinical symptom assessment, adverse/ device event assessment, documentation of any re-intervention (as applicable)* ○ *If acute cholecystitis is not resolving or not improving, a CT with contrast (unless contraindicated) will be required to rule out possible stent migration, perforation, cholangitis, sepsis or portal vein thrombosis.* • **Reintervention Visit** (if applicable): Documentation of any re-intervention (including luminal debridement), imaging (as applicable), labs (as applicable), clinical symptom assessment, stent placement (as applicable), stent removal (as applicable), stent patency assessment (as applicable), adverse event/device event assessment, current medication(s) • **Stent Removal Procedure** (Office/Hospital Visit): at 30-60 days after stent placement in the setting of resolved acute cholecystitis (unless medically recommended otherwise, i.e. the stent remain

	indwelling indefinitely): stent removal, adverse event/device event assessment, documentation of any re-intervention (as applicable), stent patency assessment, clinical symptom assessment, current medication(s) *Note: After stent removal, the physician will continue to treat the patient per standard of practice* • **72 Hour Post-Stent Removal Visit** (+24 hours) (Telephone): adverse event assessment, documentation of any re-intervention (as applicable), current medication(s) • **End of Study Visit** (Office/Hospital Visit): at 30 days (+/- 7 days) post stent removal or 90 days (+/- 14 days) post stent placement (whichever comes first) for patients with an AXIOS™ stent implanted; 30 days post-resolution of cholecystitis or 60 days post-index procedure (whichever comes first) for patients without an AXIOS™ stent implanted: clinical symptom assessment, laboratory markers of inflammation or cholestasis, adverse event assessment, documentation of any re-intervention (as applicable), current medications • **Additional visits as needed**: Adverse events assessment / device event assessment, imaging (as applicable), labs (as applicable), documentation of any re-intervention (as applicable), current medication
Study Duration	Subjects will be on study for up to 15 weeks
Key Inclusion Criteria	1. Patient requiring intervention for the management of symptoms associated with acute cholecystitis 2. Patients referred for percutaneous drainage of the gallbladder who are not surgical candidates because of advanced age, anesthetic risk, significant co-morbidities and/or overall health 3. Eligible for endoscopic intervention 4. Acute Cholecystitis (AC) Grade I (mild) or II (moderate) per Tokyo guidelines [3]: • AC Grade I (mild) defined as acute cholecystitis in an otherwise healthy patient with mild local inflammatory changes and without organ dysfunction. Criteria for grade II or III not met. • AC Grade II (moderate) defined by any one of the following characteristics o Leukocytosis (>18,000 cells per mm^3) o Palpable, tender mass in right upper quadrant o Symptom duration >72 hours

	○ Marked local inflammation (gangrenous or emphysematous cholecystitis, pericholecystic or hepatic abscess, biliary peritonitis) 5. Pre-drainage imaging confirms sufficient stone-free space to allow AXIOS™ stent deployment and complete flange expansion 6. 18 years of age or older 7. Willing and able to comply with the study procedures and patient or legally authorized representative (LAR) must provide written informed consent form (ICF) to participate in the study
Key Exclusion Criteria	1. AC Grade III (severe) per Tokyo guidelines [3] defined by organ dysfunction in any one of the following systems: • Cardiovascular - Hypotension requiring administration of ≥5μg/kg/min of dopamine or any dose of norepinephrine • Neurologic - Decreased level of consciousness • Respiratory - PaO_2/FiO_2 <300 • Renal - Oliguria and Creatinine >2.0 mg/dl (>177 μmol/liter) • Hepatic - International normalized ratio >1.5 • Hematologic - Platelet count <100,000/mm3 2. Obvious signs on diagnostic imaging of perforated, extensive gangrenous or ischemic gallbladder [44, 45]. 3. Hepatic abscess 4. Ascites 5. Patients with abnormal coagulation or who require ongoing complete anticoagulation 6. Bleeding diathesis 7. History of surgical treatment of acute cholecystitis (e.g. cholecystectomy) 8. Patients with a current percutaneous drainage 9. Patients with a history of percutaneous gallbladder drainage without AC free period following percutaneous drainage removal 10. Distance between gallbladder wall and duodenal or gastric wall >1cm by US (ultrasound) at the time of drainage 11. Patients with intervening gastric varices or vessels within a one centimeter radius of the device insertion location 12. Patients that have allergies or are sensitive to any of the device materials 13. Patients with contraindications to use of electrical devices

	14. Pregnancy 15. Prisoners and other vulnerable populations
Statistical Methods	
Statistical Test Method for the Primary Effectiveness Endpoint	The analysis of the primary effectiveness endpoint is to compare the days to clinical resolution using an AXIOS™ Stent to a performance goal (PG). The null and alternative hypotheses for the primary effectiveness endpoint analysis are as follows: H_0: $\mu_{days} \geq PG$ H_1: $\mu_{days} < PG$ where μ_{days} is the mean days to clinical resolution for patients in the AXIOS™ Gallbladder Drainage Study and PG is a performance goal of 3.5 days based on a literature review of percutaneous drainage studies.
Sample Size Parameters	This analysis of the primary effectiveness endpoint is to compare the observed days to clinical resolution for AXIOS™ stents from this study to a PG. • Expected AXIOS™ stent (test) mean days to clinical resolution = 2.35 days with standard deviation 2 days (point estimate of days to clinical resolution based on rates reported in literature [4] with median days to clinical response of 1 day, range 0 to 3 days) • PG = 3.5 days (mean days to resolution for percutaneous GB drainage based on historical rates reported in literature [5]) • Test significance level (α) = 0.022 (1-sided) • Power (1-β) = 80.4% • Evaluable number of patients needed = 27 • Expected rate of attrition = 10% • Enrolled number of patients = 30
Success Criteria for the Primary Effectiveness Endpoint	For the primary effectiveness endpoint of days to clinical resolution, testing will be performed as described below. The mean time to resolution and standard error of the mean will be estimated from a Kaplan-Meier analysis so that subjects for whom resolution is not obtained can be included in the analysis.

	The estimated mean and standard error from the Kaplan-Meier analysis will be used to construct a one-sided 97.8% upper confidence bound of the mean. If the upper 97.8% confidence bound of the mean days to clinical resolution for the AXIOS™ group is less than the performance goal of 3.5 days, the null hypothesis will be rejected in favor of the alternative hypothesis and the mean days to resolution for the AXIOS™ group will be considered to be significantly less than the performance goal of 3.5 days.
Secondary Effectiveness Endpoint	The null and alternative hypotheses for the secondary effectiveness endpoint are as follows: H_0: $\pi_{reint} \geq PG$ H_1: $\pi_{reint} < PG$ where π_{reint} is the rate of reintervention for patients in the AXIOS™ Gallbladder Drainage Study and PG is a performance goal of 46.2% based on reintervention rates associated with percutaneous drainage reported in literature [19, 41].
Sample Size Parameters	This analysis of the secondary effectiveness endpoint is to compare the observed rate of reintervention for AXIOS™ stents from this study to a PG. • Expected AXIOS™ stent (test) rate of reintervention = 8.0% (point estimate of rate of reintervention based on historical rates reported in literature [19, 41]) • PG = 46.2% (rate of reintervention for percutaneous GB drainage based on historical rates reported in literature [19, 41]) • Test significance level (α) = 0.003 (1-sided) • Power (1-β) = 99% • Evaluable number of patients needed = 27 • Expected rate of attrition = 10% • Enrolled number of patients = 30
Success Criteria for the Secondary Effectiveness Endpoint	For the secondary effectiveness endpoint of rate of reintervention, testing will be performed as described below. If the *P* value from the one-group binomial test comparing the rate of reintervention from the AXIOS™ stent to the performance goal is <0.003, the rate of reintervention for the AXIOS™ group will be concluded to be significantly less than the performance goal for the analysis set being tested. This corresponds to the one-sided Clopper-Pearson upper 99.7% confidence bound on the rate of reintervention for the AXIOS™ group being less than the performance goal of 46.2%.

Table of Contents

1 Introduction

1.1 *Background*

Acute cholecystitis is one of the most common complications of gallstone disease [7,8]. In patients affected by acute cholecystitis, percutaneous transhepatic drainage of the gallbladder (PT-GBD) using a thin plastic tube (catheter), that allows the bile to drain into a collection bag outside the body, is considered the standard of care when the patients are at high risk for cholecystectomy [9]. In these patients percutaneous cholecystostomy (PC) can act either as a bridging procedure to cholecystectomy or as a definitive treatment in those who are permanently medically unfit for surgery [10]. However, this procedure is associated with catheter migration, or dislodgement including inadvertent or intentional removal by patients, requiring numerous re-interventions [11-13] in order to reach clinical resolution of acute cholecystitis (average of 5.4 days) [5,46,47]. Additionally, percutaneous cholecystostomy is associated with a high rate of complications. Bile leaks that could result in peritonitis, bleeding, pneumothorax, recurrent cholecystitis, and secondary infection are among the most common complications of percutaneous gallbladder drainage [4,14,15].

The issues associated with percutaneous drainage, as described above, led physicians to develop an alternative procedure called endoscopic ultrasound-guided transmural gallbladder drainage (EUS-GBD). EUS-GBD is non-surgical, endoscopic procedure, whereby a stent is placed in the gallbladder to allow bile to directly drain into the gastrointestinal tract. EUS-GBD has the potential to eliminate some of the shortcomings of PC [2], and possibly ameliorate the quality of life in these high-risk, non-surgical patients by excluding the need for an external drain and reducing the number of procedural re-interventions.

Historically EUS-GBD was first performed with small diameter plastic stents, and later with self-expanding metal stents (SEMS) that were designed for use in other indications and were not developed specifically for transmural placement. Although such EUS-GBD methods provided many advantages associated with an internal drain, the complication rates were not optimal.

More recently, lumen apposing metal stents (LAMS), such as the AXIOS™ Stent with Electrocautery Enhanced Delivery System, which was specifically designed for transmural placement and internal drainage between two organs, have started to be used for GB drainage in patients with acute cholecystitis. The AXIOS™ system includes a silicone-covered, bilaterally flanged nitinol stent and an electrocautery enabled delivery system that allows one-step placement of the device without a need for ancillary procedures. Nine (9) publications [4,16-23] representing 264 patients suggest that AXIOS™ has a low risk of procedure related mortality (3.0%) while offering the advantages of internal gallbladder drainage in the setting of acute cholecystitis (**Appendix 24.1**).

Complications of PC, especially in critically ill, high-risk surgical patients, may contribute to higher morbidity than in patients treated with EUS-GBD; especially due to the high rate of re-interventions required. This is documented in three head to head studies comparing the outcome of EUS-GBD using LAMS with that of PT-GBD (**Appendix 24.2**). One of these 3 publications does not explicitly state that AXIOS™ LAMS was used, although the figures in

this publication are suggestive thereof. The overall complication rate is 24.7% for EUS-GBD, versus 37.8% for PT-GBD (P-value 0.16) with procedure related mortality rates of 2.9% for both procedures and clinical success rate of 93.2% for EUS-GBD, versus 89.4% for PT-GBD (P-value 0.50). In addition to these studies, a large systematic review on PC, Winbladh et al, reports a 30-day mortality of 15.4% [6] compared to a rate of 16.9% in AXIOS™. The procedure related mortality of PC is 4.0% [6] versus 3.0% in AXIOS™. These mortality rates are not statistically significant (exact P-value 0.57 and 0.37 for 30-day and procedure-related mortality, respectively). It is critical to note that Winbladh et al separately reported biliary deaths, which also fall under 'procedure mortality' [6].

Our proposed study aims to prospectively document the safety and effectiveness of the use of the AXIOS™ stent for EUS-GBD. We anticipate it will demonstrate that transmural drainage with AXIOS™, compared to historical percutaneous drainage, will result in faster resolution of acute cholecystitis, and possibly lower complication rates, thus possibly reducing the length of post procedural hospital stay. The goal is to document that EUS-GBD using AXIOS™ may be a suitable treatment alternative for patients with acute cholecystitis who are at high risk or unsuitable for cholecystectomy.

Acute Cholecystitis

Acute cholecystitis, or inflammation of the gallbladder, is a common surgical condition [24,25]. This condition often develops over a period of hours, with symptoms that include right upper quadrant pain and tenderness, fever, chills, nausea, and vomiting. Cholecystitis is a well-recognized complication of cholelithiasis (gall stones). When a stone becomes impacted in the cystic duct, blocking normal bile flow, it often causes inflammation of the gallbladder. The inflammatory processes resulting from bile stasis then perpetuates mucosal damage within the gallbladder, which leads to fluid secretion and further inflammation. If left untreated, bacterial infection, necrosis, and perforation of the gallbladder can occur. Thus, timely treatment with antibiotics and often cholecystectomy (removal of the gallbladder) is required.

Cholecystectomy

Currently, laparoscopic cholecystectomy is the gold standard of treatment for otherwise healthy patients with acute cholecystitis, and in these patients, this procedure is associated with a very low risk of morbidity and mortality [25,26]. However, there is an increased incidence of cholelithiasis with increasing age. In the United States, the overall incidence of cholelithiasis is reported to be 7.9% for men and 16.6% in women. However, the prevalence of gallbladder disease increases with age, beginning at 1.3% for men and 6.5% for women aged 20-29 and increasing to 25.3% of men and 33.1% of women between the ages of 60-74 [25]. Incidence rates in other Western countries are similar (for example, in Italy, the incidence rate of gallbladder disease in men aged 20-29 is 2.3% while in women in the same age group the incidence is 7.4%, and these incidence rates rise to 19.4% for men and 31.6% for women over the age of 60) [25]. Additionally, in the indigenous populations in the Americas the incidence of gallstone disease is especially high, particularly in the Malpuche Indian population in Chile. In this population, the incidence of gallbladder disease approaches 50% in women over 50 years of age [25]. This presents a dilemma for the treating physician, because for elderly patients or patients with other serious underlying

comorbidities, laparoscopic cholecystectomy can be associated with significant risk of morbidity (up to 41%) [27-29] and mortality (up to 19%) [6]. Thus, these patients are usually not considered for cholecystectomy. In such patients, surgery is either delayed (which can increase the risk of eventual sepsis and death) or avoided altogether through the use of non-surgical options for gallbladder drainage. These non-surgical techniques can be used as either a bridge to surgery or as definitive treatment in patients who remain unfit for surgery.

Percutaneous Cholecystostomy

Percutaneous cholecystostomy is the most common and most studied non-surgical, second-line procedure used to drain the gallbladder and relieve symptoms of cholecystitis. However, percutaneous cholecystostomy is associated with significant morbidity as well (up to 25%) [6], and mortality (up to 60%) [32]. Adverse events associated with an external gallbladder drainage tube can occur and may include post-procedure pain and discomfort, infection, and catheter dislodgement and migration [6,25]. Catheter migration, for example, has been shown to occur in up to 12% of percutaneous cholecystostomy cases [30-33], and other adverse events, including bile leaks, bleeding, and pneumothorax have been reported to occur in about 10% of patients [19,32,33].

Endoscopic Gallbladder Drainage

Recently, endoscopic techniques for managing acute cholecystitis in high-risk patients have gained popularity. Endoscopic techniques are thought to be advantageous because they allow avoidance of both surgery and the need to place an external drainage catheter and therefore may present fewer risks to the patient [34]. Endoscopic drainage techniques include the placement of nasogallbladder catheters and transpapillary gallbladder stenting [34,35]. In addition, EUS-guided transmural gallbladder drainage procedures have been developed as another alternative option for managing cholecystitis in patients who are not surgical candidates. Transmural drainage techniques have been performed with plastic stents, self-expanding metal stents, and most recently, with novel lumen-apposing metal stents (LAMS) such as the AXIOS™ Stent with Electrocautery Enhanced Delivery System [4,34,36,37]. The AXIOS™ stent system includes a silicone-covered, bilaterally flanged nitinol stent and an electrocautery enabled delivery system that allows one-step placement of the stent.

Historically when EUS-guided drainage of the gallbladder was first attempted, there was a concern over air or bile leakage into the peritoneal cavity as a complication of the procedure since insertion of a drain or plastic stent requires a fistula tract with a diameter larger than the diameter of the inserted drain or stent [16,38]. In the beginning, when plastic stents were used for drainage, their small diameter were associated with increased risk of clogging, leading physicians to use self-expanding metal stents (SEMS) [39] which tend to occlude less frequently; however, fully covered versions of SEMS showed a higher propensity to migrate [39]. Consequently improvement in stent technology continued and eventually led to the development of a lumen apposing metal stent (LAMS). LAMS were developed to overcome the risk of bile or enteric content leakage and stent migration, more specifically a large-caliber lumen apposing metal stent would be ideal for transmural cholecystostomy [38,40]. This type of stent reduces the risk of bile and gas leakage when adherence to the gallbladder wall is lacking or indeterminate [39], eliminating the restriction of LAMS for use only in

certain complications such as gallbladder empyema whereby the gallbladder wall is attached to the GI tract.

Theoretically, the advantages to using LAMS such as AXIOS™ for transmural drainage of the gallbladder rather than other stents include the LAMS' ability to oppose the gallbladder wall to the gastric or intestinal lumen, which can prevent possible bile leaks and also prevent migration of the stent. The silicone covering of AXIOS™ may also prevent tissue ingrowth into the stent, which allows the stent to be removed more easily when needed. Finally, the large lumen diameter of the AXIOS™ stent could allow passage of an endoscope into the gallbladder, which can then be used to perform lithotripsy to break up and remove remaining large gallstones residing in the gallbladder.

AXIOS™ Stents for EUS-GBD, and Comparisons with PT-GBD

In 9 published studies consisting of a total of 264 patients, gallbladder drainage was performed using a lumen apposing metal stent, AXIOS™, to treat patients with acute cholecystitis [4,15-22]. In these 264 patients, there were two (0.76%) cases of peritonitis [17,19]. These studies have demonstrated that there is no longer a significant risk of developing peritonitis when treating patients with acute cholecystitis, nor gallbladder empyema, by EUS-GBD with LAMS. In addition, these studies document that in cases in which the AXIOS™ stent was removed after resolution of acute cholecystitis, there were no serious late complications in patients with a follow-up period of up to 19 months [22]. However, in most cases the LAMS are left in place in order to reduce the number of interventions primarily due to the poor clinical condition of these patients. A prospective study reports a mean indwell time of 364 days using AXIOS™ with no device related adverse events reported [16].

Published evidence suggests that EUS-GBD, using lumen apposing metal stents, is a feasible and safe alternative to percutaneous gallbladder drainage (PT-GBD) choice for patients unsuitable for cholecystectomy. Technical success (correct and successful placement of stent), clinical success (resolution of acute cholecystitis), post-procedural pain, the number of additional interventions needed to reach clinical success, and post-procedural hospital stay, are among some of the variables analyzed in studies comparing EUS-GBD with percutaneous gallbladder drainage [17,18,41]. None of these variables have shown to be unfavorable towards EUS-GBD. An analysis of the data yields no statistical difference in the technical success and clinical success rate of EUS-GBD versus PC (96.6% vs 99.5%) and (93.2% vs 89.4%) respectively, (p value 0.85 and 0.50), [Appendix 24.2]. However, there is a trend towards lower complications for EUS-GB vs. PC (24.7% vs. 37.8%). Among all variables, the most prominent difference between the two procedures is in the average number of subjects that require additional interventions to resolve acute cholecystitis. In the aforementioned studies only an overall average of 8.0% of EUS-GBD patients required additional interventions, such as additional endoscopic sessions or surgery, in comparison to an average of 46.2% of patients who were required to undergo further procedures post initial PT-GBD.

To date there are 3 medical device reporting (MDR) submissions related either to the AXIOS™ stent or to the placement procedure that had fatal outcomes (1 Netherlands, 1 China, 1 USA). The fatalities were due to aspiration pneumonia, bile peritonitis, and one

death that was possibly related to either pancreatic cancer or infection. Of these, two are included in the literature rates mentioned previously, namely bile peritonitis and aspiration pneumonia [15]. Death due to aspiration pneumonia, infection, and bile peritonitis have all been reported in PC literature [9,11,42,43], and bile leaks that could result in peritonitis are among the most common complications of percutaneous gallbladder drainage [4,14,15]; however they seem to occur less frequently with AXIOS™ (only two cases in literature report a patient developing bile peritonitis, one of which was successfully resolved) [17, 19].

Two studies [19,23] provide safety and efficacy data for AXIOS™ as well as parameters that are not recorded in most studies with AXIOS™ such as pain, and post procedural hospital stay. Irani et al., a large retrospective study, examines outcomes of 45 subjects that underwent EUS-GBD using AXIOS™ and 45 subjects that underwent PT-GBD for acute cholecystitis in patients who were not surgical candidates [19]. Kaheleh et al classified their subjects as poor surgical candidates, based on either a diagnosis of unresectable cancer, or multiple co-morbities that precluded surgery [23]. Irani et al's retrospective chart review included only patients who were deemed non-surgical candidates [19]. Their patient population was so critically ill, that 47% of their overall patient population passed away at follow up due to co-morbidities. Malignancy was seen to be the most common co-morbidity in these two studies. Both average pain scores and average number of patients hospitalized after the procedure were lower among AXIOS™ recipients versus those subjects who underwent PT-GBD. On average the pain scores were 2.5 vs 6.5 ($P<.05$) and 9.9% of patients were hospitalized after receiving AXIOS™ vs 40.1% of patients were hospitalized after having a PC procedure [19]. Additionally, the number of repeat interventions per patient was lower at an average of 0.2 ± 0.4 in the EUS-GBD with AXIOS™ group vs 2.5 ± 2.8 ($P<.05$), in the PT-GBD group. This study concludes on an overall lower pain score, shorter hospital stay, and fewer repeat interventions for unsuitable surgical candidates undergoing EUS-GBD using AXIOS™ in comparison to those undergoing PT-GBD. Kahaleh et. al. reports on an international collaborative study of 35 patients who underwent EUS-GBD, 15 of which received the AXIOS™ stent [23]. An overall EUS-GBD technical success rate of 97.2%, clinical success rate of 92%, and a low re-intervention rate of 9.4%, suggest that EUS-GBD using LAMS might be a suitable alternative to PT-GBD in critically ill, non-surgical candidates suffering from multiple co-morbidities and/or advanced malignancies.

1.2 Rationale for Study

In conclusion, data suggests that treatment of critically ill, non-surgical candidates with EUS-GBD using the AXIOS™ stent results in clinical resolution of their acute cholecystitis coupled with a better quality of life resulting from shorter post-procedural hospital stay, lower post-procedural pain scores, and most notably – fewer post-procedural interventions. We propose a multi-center single arm prospective study in 30 patients to confirm the safety and efficacy of AXIOS™ for EUS-GBD in patients referred to percutaneous drainage of the gallbladder due to advanced age, anesthetic risk, significant co-morbidities and/or overall health.

2 Device Description

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. The AXIOS™ Stent and Electrocautery-Enhanced Delivery System is intended for single use and is provided sterile using ethylene oxide.

The study device is indicated for use to facilitate drainage of the biliary tract (which includes the gallbladder) outside of the U.S. The study device is not approved for gallbladder drainage in the U.S. and will be considered investigational for this indication. Local Ethics Committee (EC)/Institutional Review Board (IRB)/Research Ethics Board (REB) 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 and expiration date. 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	Overall Stent Length	Flange Diameter	
Electrocautery Enhanced AXIOS™ System with 10x10 Stent	10 mm	10 mm	20 mm	21 mm	10.8Fr
Electrocautery Enhanced AXIOS™ System with 15x10 Stent	15 mm	10 mm	20 mm	24 mm	10.8Fr

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

2.1 *Device Use*

Current cleared indication for use: The AXIOS™ Stent and Electrocautery Enhanced Delivery System is cleared in the US "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 are 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 in the U.S. for this IDE study: The AXIOS™ Stent and Electrocautery Enhanced Delivery System is intended for endoscopic ultrasound-guided transluminal gallbladder drainage in patients with acute cholecystitis who are at high risk or unsuitable for surgery.

3 Study Objective

To evaluate the safety and effectiveness of the AXIOS™ Stent with Electrocautery Enhanced Delivery System in the management of symptoms of acute cholecystitis as an alternative to percutaneous gallbladder drainage.

4 Endpoints and Study Design

4.1 *Primary Effectiveness Endpoint*

The primary effectiveness endpoint is time to resolution of acute cholecystitis which will be measured in days. Resolution is defined as either a fever of less than 100.5°F, or at least a 4-point decrease in the pain score, or WBC count less than 12,000/cc, with improvement in at least two of these categories without the deterioration of the third category.

4.2 *Secondary Effectiveness Endpoint*

The secondary effectiveness endpoint is the rate of re-interventions including but not limited to stent migration, stent occlusion by GB stones, and luminal debridement.

4.3 *Additional Endpoints*

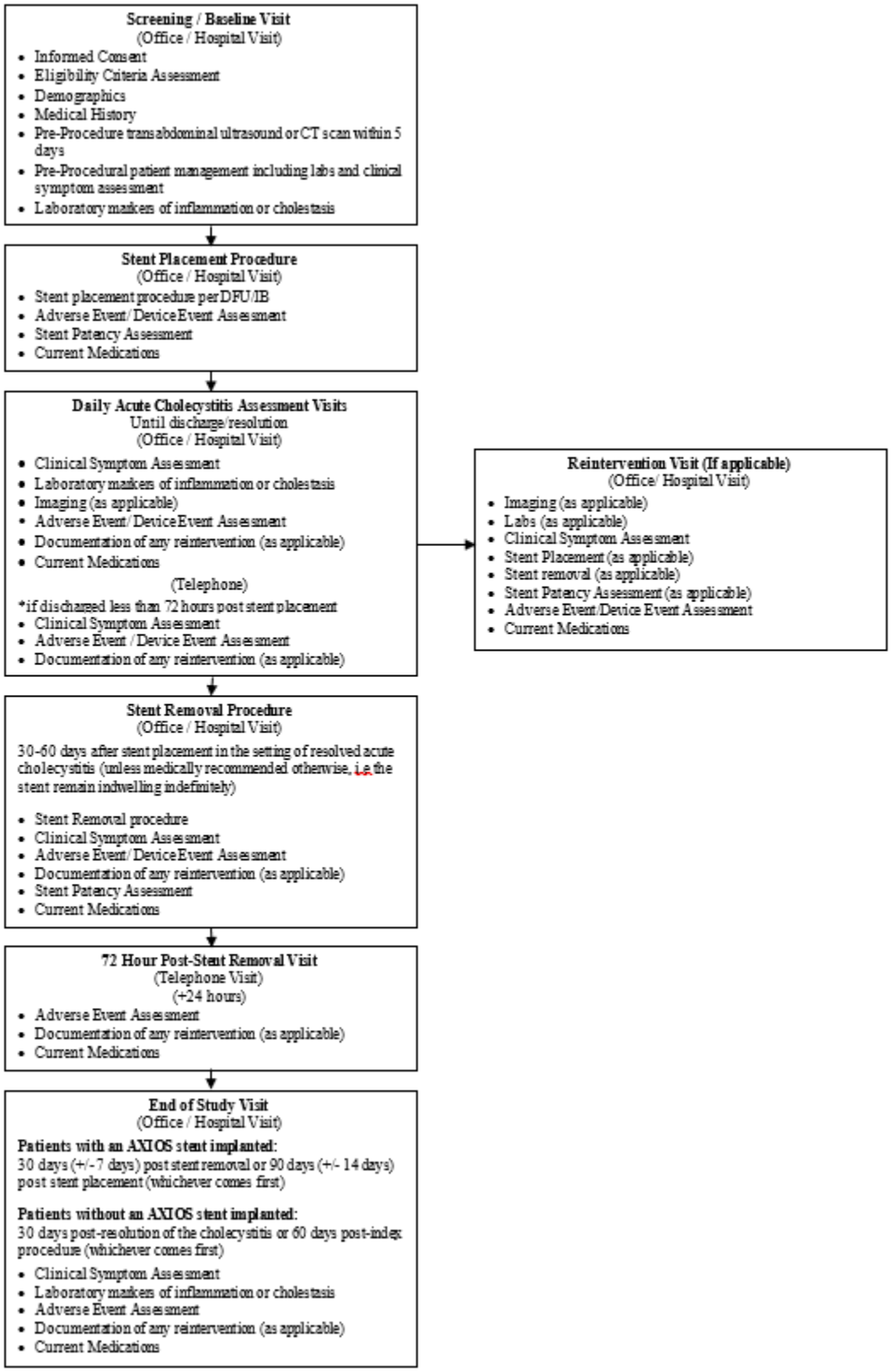
1. Stent patency (ability to facilitate gallbladder drainage) defined indirectly as resolution of acute cholecystitis or, in the absence of resolution of acute cholecystitis, endoscopic observation of unobstructed AXIOS™ stent lumen
2. Technical stent placement success: Successful stent placement, defined as transmural placement of the AXIOS™ stent with confirmed stent patency via (i) drainage visualized through the stent or fluoroscopically, or (ii) ability to endoscopically observe the inner walls of the gallbladder through the AXIOS™ stent
3. Technical stent removal success: Successful stent removal, defined as ability to remove the AXIOS™ stent endoscopically without stent removal related serious adverse events
4. Rate of recurrence of acute cholecystitis and its management

5. Number of cumulative hospital and ICU days from initial stent placement to resolution of symptoms of acute cholecystitis.

4.4 *Study Design*

This study is a prospective, multi-center, single arm, consecutive series study. Treatment of up to 30 subjects will take place at up to 9 clinical centers. Subjects who meet all eligibility criteria will receive the AXIOS™ stent for up to 8 weeks stent indwell (unless medically recommended otherwise, i.e. the stent remain indwelling indefinitely) and 30-day follow-up after stent removal.

Figure 4.4-1: AXIOS™ for GB 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 criterion is met.

1. Patients requiring intervention for the management of symptoms associated with acute cholecystitis
2. Patients referred to percutaneous drainage of the gallbladder who are not surgical candidates because of advanced age, anesthetic risk, significant co-morbidities and/or overall health
3. Eligible for endoscopic intervention
4. Acute Cholecystitis, Grade I (mild) or II (moderate) per Tokyo guidelines [3]:
   - AC Grade I (mild) defined as acute cholecystitis in an otherwise healthy patient with mild local inflammatory changes and without organ dysfunction. Criteria for grade II or III not met.
   - AC Grade II (moderate) defined by any one of the following characteristics
     - Leukocytosis (>18,000 cells per mm^3)
     - Palpable, tender mass in right upper quadrant
     - Symptom duration >72 hours
     - Marked local inflammation (gangrenous or emphysematous cholecystitis, pericholecystic or hepatic abscess, biliary peritonitis)
5. Pre-drainage imaging confirms sufficient stone-free space to allow AXIOS™ stent deployment and complete flange expansion
6. 18 years of age or older
7. Willing and able to comply with the study procedures and patient or Legally authorized representative (LAR) must provide written informed consent form (ICF) to participate in the study

5.2 *Exclusion Criteria*

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

1. AC Grade III (severe) per Tokyo guidelines [3] defined by organ dysfunction in any one of the following systems:
   - Cardiovascular - Hypotension requiring administration of ≥5μg/kg/min of dopamine or any dose of norepinephrine
   - Neurologic - Decreased level of consciousness
   - Respiratory - PaO_2/FiO_2 <300
   - Renal - Oliguria and Creatinine >2.0 mg/dl (>177 μmol/liter)
   - Hepatic - International normalized ratio >1.5
   - Hematologic - Platelet count <100,000/mm3

2. Obvious signs on diagnostic imaging of perforated, extensive gangrenous or ischemic gallbladder [44, 45]
3. Hepatic abscess
4. Ascites
5. Patients with abnormal coagulation or who require ongoing complete anticoagulation
6. Bleeding diathesis
7. History of surgical treatment of acute cholecystitis (e.g. cholecystectomy)
8. Patients with a current percutaneous drainage
9. Patients with a history of percutaneous gallbladder drainage without AC free period following percutaneous drainage removal
10. Distance between gallbladder wall and duodenal or gastric wall > 1cm by US (ultrasound) at the time of drainage
11. Patients with intervening gastric varices or vessels within a one centimeter radius of the device insertion location
12. Patients that have allergies or are sensitive to any of the device materials
13. Patients with contraindications to use of electrical devices
14. Pregnancy
15. Prisoners and other vulnerable populations

6 Subject Accountability

6.1 *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.

6.2 *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. 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.

6.3 *Lost to Follow-Up*

A subject will be considered lost to follow-up if the subject remains unresponsive to communication after three documented attempts by study staff. (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods).

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). These contact attempts should be documented in the subject's medical record or study file.

Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.4 *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. Subjects in the ITT cohort will be counted towards the enrollment ceiling and this cohort will be considered the primary analysis cohort.

Treated Cohort

The treated cohort is defined as all ITT subjects who have an AXIOS™ stent implanted for the purpose of gallbladder drainage.

Per Protocol Cohort

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

6.5 *End of Study Definition*

A clinical trial is considered completed when ***subjects*** are no longer being examined or the last ***subject***'s last study visit has occurred.

7 Study Methods

7.1 *Data Collection*

Procedure / Assessment	Screening / Baseline Visit	Stent Placement Procedure	Daily Acute Cholecystitis Assessment Visits (until discharge/ resolution)	Reintervention Visit (if applicable)	Stent Removal Procedure: 30 – 60 days post stent placement (prompted by resolved Acute Cholecystitis)	72hr (+24hr) post Stent Removal Visit	End of Study Visit*
Informed Consent	X						
Eligibility Criteria Assessment	X						
Demographics	X						
Medical History	X						
Imaging**	X	X (as applicable)	X (as applicable)	X (as applicable)			
Clinical Symptom Assessment	X		X	X	X		X
Pre-Procedure Subject Management	X						
Stent Placement		X		X (as applicable)			
Documentation of any Reintervention			X (as applicable)	X	X (as applicable)	X(as applicable)	X (as applicable)
Labs	X		X	X (as applicable)			X
Current Medications***	X	X	X	X	X	X	X
Stent Removal				X (as applicable)	X		
Stent Patency Assessment		X		X (as applicable)	X		
Adverse Events Assessment		X	X	X	X	X	X
Device Events Assessment		X	X	X	X		

X – Required
* 30 days (+/- 7 days) post stent removal or 90 days (+/- 14 days) post stent placement, whichever comes first, for patients with an AXIOS stent implanted; 30 days post-resolution of cholecystitis or 60 days post-index procedure, whichever comes first, for patients without an AXIOS stent implanted
** Diagnostic imaging may include CT with contrast (unless contraindicated), transabdominal ultrasound, MRI, EUS, fluoroscopy with contrast, hepatobiliary scintigraphy (HIDA scan).
*** all anticoagulants, antiplatelet agents, antibiotics, and pain medications

7.2 *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 Electronic Data Capture (EDC) by the center to document select information about candidates who signed consent.

7.3 *Informed Consent*

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

7.4 *Visit Schedule*

Screening / Baseline – Office/Hospital Visit:

- Informed Consent
- Eligibility Criteria Assessment
- Demographics
- Medical History
- Pre-Procedure imaging within 5 days of drainage procedure (CT scan or transabdominal ultrasound)

  Note: If there has been a deterioration of the patient's clinical status or worsening of the patients' liver chemistry profile since the most recent pre-procedure imaging, then additional imaging is needed to evaluate if the patient is still a candidate for the intervention.

- Current Medications
- Pre-Procedure subject management including labs and clinical symptom assessment
  - Laboratory markers of inflammation or cholestasis
    - White Blood Cells (WBC)
    - Hemoglobin
    - Alanine aminotransferase

- Alkaline phosphatase
- C reactive protein
- Bilirubin

Stent Placement Procedure – Office/Hospital Visit

- Stent Placement
- Imaging (as applicable)
- Adverse Events Assessment / Device Event Assessment
- Stent Patency Assessment
- Current Medications

Note: See DFU/ IB and Additional Procedural Notices below for procedure guidance.

Additional Procedural Notices:

- *Procedure should be done with CO_2 insufflation.*
- *Choice of placement of stent between the duodenum and the gallbladder or between the stomach and the gallbladder is left at discretion of treating physician.*
- *Physicians will select the site of the AXIOS™ stent placement under EUS guidance and choose an access location where there is*
  - *adequate stone-free space within the gallbladder to deploy the flange*
  - *distance between the gallbladder and the stomach or duodenal lumen that does not exceed 10mm, the saddle length of the AXIOS™ stent*
  - *no intervening ascites, bowel, or fat, as identified by EUS*
- *If a patient's gallbladder has minimal stone burden and is free of large stones per baseline imaging, a 10mm lumen diameter AXIOS™ stent is recommended*
- *If a patient's gallbladder is packed with stones or large stones (1cm or larger in diameter) are present per baseline imaging, a 15mm lumen diameter AXIOS™ stent is recommended*
- *Stones and/or sludge will be cleared using gentle basketing and irrigation through the stent if necessary, at the discretion of investigator*
- *Placement of double pigtail plastic stent(s) through AXIOS™ will not be allowed in the study.*
- *If placement of the AXIOS™ stent is attempted but no stent placement occurs, patient will be followed until 30 days after resolution of the cholecystitis, or 60 days after the index procedure, whichever comes first. The patient's treatment will be at the discretion of the physician.*

Additional Notes:

- In case of leakage of gallbladder contents resulting from inability to place the AXIOS™ stent after puncturing the gallbladder, a second attempt will be made by placing a needle through the original enteric puncture and re-accessing the gallbladder. Once a guidewire is placed, a new AXIOS™ stent would be placed. If a second attempt to place an AXIOS™ stent is not successful, transpapillary gallbladder drainage with a cystic duct stent or percutaneous drainage may also be considered. Endoscopic closure of the

puncture site in the duodenal wall or stomach wall using conventional endoscopic techniques is advised in case of complete misdeployment and loss of puncture site access.

- In addition, percutaneous drainage of any fluid collection caused by the bile leak might be needed. If endoscopic and percutaneous approaches for the management of the gallbladder leak are unsuccessful, then surgery should be considered as soon as possible in order to avoid uncontrolled biliary peritonitis.Patients who receive an AXIOS™ stent and experience a procedural complication during stent placement will be followed until end of study, which is 30 days post stent removal or 90 days post stent placement (whichever comes first).
- In case of leakage of gallbladder or GI tract contents causing inflammation or peritonitis after the AXIOS™ placement procedure, due to early stent migration or other causes the following complication management approaches should be considered in the following sequence:
    - Administration of antibiotics and monitoring of the patient
    - Endoscopic management (e.g. ERCP)
    - Percutaneous drainage
    - Surgical closure of the leak and gallbladder drainage
- In case of AXIOS™ stent misplacement or migration, stent will be removed endoscopically.

A CT scan with contrast (unless contraindicated) will be required in all of the above-mentioned circumstances.

- The maximum stent indwell time of 30 to 60 days should be intended. This timeframe takes into consideration both the time needed for AC resolution as well as time needed for fistula formation, unless medically recommended.

Daily Acute Cholecystitis Assessment Visit (until discharge/resolution) – Office/Hospital Visit

- Clinical Symptom Assessment
- Laboratory markers of inflammation or cholestasis
    - White Blood Cells (WBC)
    - Hemoglobin
    - Alanine aminotransferase
    - Alkaline phosphatase
    - C reactive protein
    - Bilirubin
- Imaging (as applicable)

Note: CT with contrast (unless contraindicated) required if acute cholecystitis is not resolving or not improving

- Adverse Events Assessment / Device Event Assessment

- Documentation of any re-intervention, including luminal debridement (as applicable)
- Current Medications

Note: if discharged less than 72 hours post stent placement, a follow-up phone call may be done instead of an office visit and the following assessments will be made:

- *Clinical symptom assessment*
- *Adverse Events Assessment / Device Event Assessment*
- *Documentation of any re-intervention (as applicable)*

If acute cholecystitis is not resolving or not improving, a CT with contrast (unless contraindicated) will be required to rule out possible stent migration, perforation, cholangitis, sepsis or portal vein thrombosis.

Re-intervention Visit (if applicable)

- Documentation of any re-intervention, including luminal debridement
- Imaging (as applicable)
- Labs (as applicable)
- Clinical Symptom Assessment
- Stent Placement (as applicable)
- Stent Removal (as applicable)
- Stent Patency Assessment (as applicable)
- Adverse Events Assessment/Device Event Assessment
- Current Medications

Stent Removal Procedure (30-60 days after stent placement in the setting of resolved acute cholecystitis unless medically recommended otherwise, i.e. the stent remain indwelling indefinitely) – Office/Hospital Visit

- Stent Removal (prompted by resolution of acute cholecystitis)
- Clinical Symptom Assessment
- Adverse Events Assessment / Device Event Assessment
- Documentation of any re-intervention (as applicable)
- Stent Patency Assessment
- Current Medications

Note: After stent removal, the physician will continue to treat the patient per standard of practice.

72 Hour (+24 hours) Post-Stent Removal Visit – Telephone Visit

- Adverse Events Assessment
- Documentation of any re-intervention (as applicable)
- Current Medications

End of Study Visit – Office/Hospital Visit

30 days (+/- 7 days) post stent removal or 90 days (+/- 14 days) post stent placement (whichever comes first) for patients with an AXIOS stent implanted.

30 days post-resolution of the cholecystitis or 60 days post-index procedure (whichever comes first) for patients without an AXIOS stent implanted.

- Clinical Symptom Assessment
- Laboratory markers of inflammation or cholestasis
  - White Blood Cells (WBC)
  - Hemoglobin
  - Alanine aminotransferase
  - Alkaline phosphatase
  - C reactive protein
  - Bilirubin
- Adverse Events Assessment
- Documentation of any re-intervention (as applicable)
- Current Medications

Additional visits as needed

- Adverse Event assessment / Device Event assessment
- Labs (as applicable)
- Imaging (as applicable)
- Documentation of any re-intervention (as applicable)
- Current Medications

7.5 *Scoring System*

Patients will be asked to report on the average pain experienced since the prior visit when reporting pain via VAS (can be done verbally).

7.6 *Study Completion*

Subjects will be followed for 30 days 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.

7.7 *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 lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

8 Statistical Considerations

8.1 *Primary Effectiveness Endpoint*

The primary effectiveness endpoint is the time to resolution of acute cholecystitis measured in days.

Statistical Test Method:

The analysis of the primary effectiveness endpoint is to compare the days to clinical resolution using an AXIOS™ stent to a performance goal (PG).

The null and alternative hypotheses for the primary effectiveness endpoint analysis are as follows:

H_0: $\mu_{days} \geq PG$

H_1: $\mu_{days} < PG$

where μ_{days} is the mean days to clinical resolution for patients in the AXIOS™ Gallbladder Drainage Study and PG is a performance goal of 3.5 days based on a literature review of percutaneous drainage studies.

Sample Size Parameters:

This analysis of the primary effectiveness endpoint is to compare the observed days to clinical resolution for AXIOS™ stents from this study to a PG.

- Expected AXIOS™ stent (test) mean days to clinical resolution = 2.35 days with standard deviation 2 days (point estimate of days to clinical resolution based on historical rates reported in literature [4] with median days to clinical response of 1 day, range 0 to 3 days)
- PG = 3.5 days (mean days to resolution for percutaneous GB drainage based on historical rates reported in literature [5])
- Test significance level (α) = 0.022 (1-sided)
- Power (1-β) = 80.4%
- Evaluable number of patients needed = 27
- Expected rate of attrition = 10%
- Enrolled number of patients = 30

The historical time to cholecystitis resolutions comes from 2 studies that report time to cholecystitis for EUS-GBD [4] and PC-GBD [5] (Table 8.1-1 and Appendix 24.2).

Table 8.1-1. Time to Cholecystitis Resolution (in days)

Reference	EUS-GBD	PC-GBD
Irani (2015) [4]	Median=1 (0-3) [N=15]	N/A
Kedia (2015) [5]	N/A*	Mean 4.6 [N=43]

* Endoscopic drainage was not transmural and therefore was not included in the analysis

Evaluation of the Primary Effectiveness Endpoint:

The primary effectiveness endpoint will be evaluated for all ITT patients regardless of whether an AXIOS™ stent is implanted. Patients for whom an AXIOS™ stent is implanted and cholecystitis is resolved will be considered a success for the endpoint and the days to resolution will be the date of resolution minus the date of the index procedure. If a patient does not receive an AXIOS™ stent, the patient will be considered a failure for the endpoint with censoring at 60 days. If a subject receiving an AXIOS™ stent does not achieve resolution of cholecystitis for any reason, the patient will be treated as censored in the Kaplan-Meier analysis and the days to censoring will be the date of censoring minus the date of the index procedure. The date of censoring will be the earliest of the following:

- date of the patient receiving a cholecystectomy,
- date of the patient dying,
- date of last contact for patients who withdraw from the study or are lost to follow-up, or
- date of the AXIOS™ stent removal.

Success Criteria for the Primary Effectiveness Endpoint:

For the primary effectiveness endpoint of days to clinical resolution, testing will be performed as described below.

The mean time to resolution and standard error of the mean will be estimated from a Kaplan-Meier analysis so that subjects for whom resolution is not obtained can be included in the analysis.

The estimated mean and standard error from the Kaplan-Meier analysis will be used to construct a one-sided 97.8% upper confidence bound of the mean. If the upper 97.8% confidence bound of the mean days to clinical resolution for the AXIOS™ group is less than the performance goal of 3.5 days, the null hypothesis will be rejected in favor of the alternative hypothesis and the mean days to resolution for the AXIOS™ group will be considered to be significantly less than the performance goal of 3.5 days.

As a worst-case scenario sensitivity analysis, the Kaplan-Meier analysis for the primary effectiveness endpoint will be re-analyzed with 60 days as the time to censoring for all censored patients with time to censoring <60 days.

8.2 *Secondary Effectiveness Endpoint*

The secondary effectiveness endpoint is the rate of re-interventions including but not limited to stent migration, stent occlusion by GB stones, and luminal debridement.

Statistical Test Method:

The analysis of the secondary effectiveness endpoint is to compare the rate of reintervention using an AXIOS™ stent to a PG.

The null and alternative hypotheses for the secondary effectiveness endpoint analysis are as follows:

H_0: $\pi_{reint} \geq PG$

H_1: $\pi_{reint} < PG$

where π_{reint} is the rate of reintervention for patients in the AXIOS™ Gallbladder Drainage Study and PG is a performance goal of 46.2% based on reintervention rates associated with percutaneous drainage reported in literature [19, 41].

Sample Size Parameters:

This analysis of the secondary effectiveness endpoint is to compare the observed rate of reintervention for AXIOS™ stents from this study to a PG.

- Expected AXIOS™ stent (test) rate of reintervention = 8.0% (point estimate of rate of reintervention based on historical rates reported in literature [19, 41])
- PG = 46.2% (rate of reintervention for percutaneous GB drainage based on historical rates reported in literature [19, 41])
- Test significance level (α) = 0.003 (1-sided)
- Power (1-β) = 99%
- Evaluable number of patients needed = 27
- Expected rate of attrition = 10%
- Enrolled number of patients = 30

The historical rates of reintervention come from 2 studies that compare the use of the AXIOS™ stent to percutaneous drainage [19, 41] (Table 8.2-1 and Appendix 24.2). The combined rate of reintervention from the AXIOS™ arms is 8.0% (7/87) and for the percutaneous drainage arms is 46.2% (73/158).

Table 8.2-1. Proportion of Patients With a Reintervention

Reference	EUS-GBD	PC-GBD
Irani (2017)* [19]	3/45 (6.7%)	45/45 (100.0%)
Tyberg (2016)** [41]	4/42 (9.5%)	28/113 (24.8%)
Total	7/87 (8.0%)	73/158 (46.2%)

*Reintervention defined as any procedure required to replace, check, or remove the previously placed drain or stent
**Reintervention defined as repeat procedure

Success Criteria for the Secondary Effectiveness Endpoint:

For the secondary effectiveness endpoint of rate of reintervention, testing will be performed as described below.

If the *P* value from the one-group binomial test comparing the rate of reintervention from the AXIOS™ stent to the performance goal is <0.003, the rate of reintervention for the AXIOS™ group will be concluded to be significantly less than the performance goal for the analysis set being tested. This corresponds to the one-sided Clopper-Pearson upper 99.7%

confidence bound on the rate of reintervention for the AXIOS™ group being less than the performance goal of 46.2%. A sensitivity analysis (ie tipping point analysis) will be done to assess the robustness of results in the case where subjects do not have resolution of cholecystitis and no reintervention was required.

8.3 *Study Success Criteria*

To declare overall study success, the null hypotheses for both the primary and secondary effectiveness endpoints must be rejected in favor of the alternative hypotheses. Since the type I errors for the primary and secondary effectiveness endpoints are 2.2% and 0.3%, respectively, the type I error for the entire study is 2.5%.

8.4 *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.

Data Analysis:

Descriptive statistics will be presented for all ITT and Treated subjects. The primary analysis for the primary and secondary effectiveness endpoints and the additional endpoints will be assessed for the ITT cohort. The primary and secondary effectiveness endpoints and the additional endpoints will also be assessed for the Treated cohort and for the PP cohort if the PP cohort is different from the Treated 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 for the ITT cohort.

Interim Analysis:

No formal interim analyses are planned for this study.

Subgroup Analysis:

There are no planned subgroup analyses.

Justification of Pooling:

The analyses will be performed using data pooled across institutions. An assessment of the poolability of subjects across sites for the primary and secondary effectiveness endpoints will be made by fitting an analysis of variance (ANOVA) model and logistic regression model, respectively, with site as a factor and the primary endpoint as outcome. The following baseline variables will also be explored for pooling: region (US or outside US), acalculous/calculous cholecystitis, grade I or II cholecystitis, and prior sphincterotomy.

If the P value for the site from the pooling analysis is ≥0.15, it will be concluded that the primary endpoint is not different across sites, and the data can be pooled. If the P value for site from the ANOVA model is <0.15, site 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 to performing the analyses 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.

9 Data Management

9.1 *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (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 clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. 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.

9.2 *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. 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.

10 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.

11 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, site re-training, or site discontinuation) will be put into place by the sponsor.

12 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 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.

13 Compliance

13.1 *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, 21CFR 814.20 part 56, part 50 and part 812 or 813, 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. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC/REB or regulatory authority shall be followed, if appropriate.

13.2 *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 Investigator Agreement 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) and potential Unanticipated Serious Adverse Device Event (USADE) or Unanticipated Adverse Event (UADE).
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- 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 Informed Consent Form (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.

13.2.1 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 a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

13.3 *Institutional Review Board/ Ethics Committee*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

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.

Any amendment to the protocol will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent, using a previously approved ICF. Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

13.4 *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 confidential 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 this information. 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 performance of its device, new medical research and proposals for developing 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 subjects.

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

13.5 *Insurance*

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

14 Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the 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.

15 Committees

An independent data review (IDR) board comprised of physician experts in surgery, interventional radiology, and gastroenterological endoscopy not participating in the clinical study and with no affiliation with BSC, will provide external oversight and review for potential safety concerns.

During the course of the clinical study, the IDR board will periodically review aggregate safety data to monitor for the incidence of major adverse events and other trends. They will assess the AEs that are reported as Serious AEs that are unrelated, unlikely related, possibly related, probably related or related to the AXIOS™ stent or the AXIOS™ stent placement or removal procedures. The IDR will also review the incidence of such AEs.

Any IDR recommendations for clinical study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to BSC for consideration.

16 Potential Risks and Benefits

16.1 *Anticipated Adverse Events and 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 gallbladder 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 gallbladder or GI tract 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 gallbladder after removal (fistula)
- Unintended electrical shock, muscle stimulation or burns
- Cardiac arrhythmia or arrest
- Death

16.2 *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research

procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.3 *Anticipated Benefits*

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

16.4 *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.

17 Safety Reporting

17.1 *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 Adverse Events
- All Serious Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects/ Unanticipated Serious Adverse Device Effects*
- New findings/updates in relation to already reported events

* BSC Medical Safety will be responsible for all UADE/USADE 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 17.2-1 for AE definitions).

Refer to Section 16 for the known risks associated with the study device(s).

17.2 *Definitions and Classification*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 17.2-1: 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* *Ref: 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 o 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. •

Table 17.2-1: Safety Definitions

Term	Definition
	NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	A 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

Refer to Section 16 for the known risks associated with the study device(s).

17.3 *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device, study stent placement procedure, and study stent removal procedure. See criteria in Table 17.3-1:

Table 17.3-1: Criteria for Assessing Relationship of Study Device or Procedure 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 re-introduction 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 be explained by another cause, but additional information may be obtained.
Causal	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; 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);

Table 17.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
	- the discontinuation of medical device application (or reduction of the level of activation/exposure) and re-introduction 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.

17.4 *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 17.4-1.

Table 17.4-1: 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
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

Table 17.4-1: 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)
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete 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.

17.5 *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, user errors, product nonconformities, and labeling errors) will be documented and reported to BSC on the eCRF. 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.

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

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

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

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

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

19 Suspension or Termination

19.1 *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.

19.1.1 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.

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

Any investigator, or 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.

20 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 an 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 investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

20.1 *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 investigator 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.

21 Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, 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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23 Abbreviations and Definitions

Acronym	Definition
AC	Acute Cholecystitis
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CE	Conformité Européene
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
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS	Endoscopic Ultrasound
EUS-GBD	Endoscopic Ultrasound Gallbladder Drainage
FDA	Food and Drug Administration
GB	Gallbladder
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Hemoglobin
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
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-To-Treat
LAMS	Lumen-Apposing Metal Stents
PC	Percutaneous Cholecystostomy
PT-GBD	Percutaneous Gallbladder Drainage
PG	Performance Goal
PP	Per-Protocol
SADE	Serious Adverse Device Event
SAE	Serious Adverse Events
SEMS	Self-Expanding Metal Stents
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

24 Appendices

24.1 *AXIOS™ EUS-GBD with Comparison to PC (Windbladh et al 2009)*

	1st Author, Year	# of Patients	30 Day Mortality (%)	Biliary/ Procedure Mortality (%)	Technical Success	Clinical Success
Axios	Itoi et al 2012 [22]	5	0/5 (0%)	0/5 (0%)	5/5 (100%)	5/5 (100%)
	de la Serna-Higuera et al 2013 [18]	13	0/13 (0%)	0/13 (0%)	11/13 (85%)	11/11 (100%)
	Walter et al 2016 [16]	30	5/30 (17%)	4/30 (13.3%)	27/30 (90%)	26/27 (96%)
	Irani et al 2015 [4]	15	2/15 (13%)	0/15 (0%)	14/15 (93%)	15/15 (100%)
	Law et al 2016 [21]	7	3/7 (42%)	0/7 (0%)	7/7 (100%)	7/7 (100%)
	Kahaleh et al 2016 [23]	15	0/15 (0%)	0/15 (0%)	13/15 (87%)	13/15 (87%)
	Irani et al 2017 [19]	45	23/45 (51%)	1/45 (2.2%)	44/45 (96%)	43/45 (96%)
	Dollhopf et al 2017 [20]	75	7/75 (9%)	0/75 (0%)	74/75 (98.7%)	71/74 (95.9%)
	Teoh et al 2017** [17]	59	1/38 (1.7%)*	1/38 (1.7%)*	57/59 (96.6%)	53/59 (89.8%)
	Axios Total	264	41/243	6/243	252/264	244/264
	Axios Average	**264**	**16.9%**	**3.0%**	**95.5%**	**92.4%**
PC	**Average PC Rates [6]**	**1870**	**15.4%**	**4.0%**	**98.9%**	**86.0%**
Axios vs PC	**Axios vs PC** Fisher' Exact p-value		**0.57**	**0.37**	**0.0002**	**0.003**

** Of 59 patients in Teoh et al 2017, 21 were already reported in Walter et al 2015, procedure mortality and 30-day mortality represents the 38 cases of Teoh 2017 that were not reported in Walter 2015

*Teoh et al 2017: Procedure Mortality – 2 cases (1 overlaps with Walter et al 2015; 1 (Aspiration Pneumonia)

24.2 *EUS-GBD VS. PTGBD*

1st Author, Year	# subjects EUS-GBD	# subjects PCGBD	Technical Success EUS-GBD	Technical Success PCGBD	Clinical Success EUS-GBD	Clinical Success PCGBD	# AE's EUS-GBD	# AE's PCGBD
Irani et al 2017 [19]	45	45	44/45 (97.8%)	45/45 (100.0%)	43/45 (95.6%)	41/45 (91.1%)	8/45 (17.8%)	14/45 (31.1%)
Teoh et al 2017 [17]	59	59	57/59 (96.6%)	59/59 (100.0%)	53/59 (89.8%)	56/59 (94.9%)	19/59 (32.2%)	44/59 (74.6%)
Tyberg et al 2016 [41]	42	113	40/42 (95.2%)	112/113 (99.1%)	40/42 (95.2%)	97/113 (85.8%)	9/42 (21.4%)	24/113 (21.2%)
Average	**146**	**217**	**96.6%**	**99.5%**	**93.2%**	**89.4%**	**24.7%**	**37.8%**

1st Author, Year	30 Day Mortality EUS-GBD	30 Day Mortality PCGBD	Procedure Mortality EUS-GBD	Procedure Mortality PCGBD	No. of subjects w/add'l interventions EUS-GBD	No. of subjects w/add'l interventions PCGBD	Overall Complications EUS-GBD	Overall Complications PCGBD
Irani et al 2017 [19]	23/45 (51.1%)	20/45 (44.4%)	1/45 (2.2%)	3/45 (6.7%)	3/45 (6.7%)	45/45 (100.0%)	8/45 (17.8%)	14/45 (31.1%)
Teoh et al 2017 [17]	5/59 (8.5%)	1/59 (1.7%)	2/59 (5.1%)	0/59 (0.0%)	NR	NR	19/59 (32.2%)	44/59 (74.6%)
Tyberg et al 2016 [41]	0/42 (0.0%)	4/113 (3.5%)	NR	NR	4/42 (9.5%)	28/113 (24.8%)	9/42 (21.4%)	24/113 (21.1%)
Average	**19.2%**	**11.5%**	**2.9%**	**2.9%**	**8.0%**	**46.2%**	**24.7%**	**37.8%**