Fully Covered Self Expanding Metal Stents (FCSEMS) for Pancreatic Duct Strictures in Patients with Chronic Pancreatitis

WallFlex Pancreatic Pivotal

CLINICAL PROTOCOL

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Protocol Synopsis

Full Title	**Fully Covered Self Expanding Metal Stents (FCSEMS) for Pancreatic Duct Strictures in Patients with Chronic Pancreatitis**
Short Title	WallFlex Pancreatic Pivotal
Objective	To prospectively document the performance of a FCSEMS for treatment of pancreatic duct strictures in patients with painful chronic pancreatitis.
Indication(s) for Use	Intended to facilitate drainage of the pancreatic duct to reduce pain in patients with painful chronic pancreatitis
Test Device	Fully Covered WallFlex Pancreatic Stent
Device Selection	Stents selected for use in this study: • Diameter: 6 mm, 8 mm • Length: 4cm, 5cm, 6cm • Type: Soft • Delivery system: Rapid Exchange
Study Design	• Prospective, single arm, multi-center • Intended WallFlex Pancreatic stent indwell duration for 6 months • Follow-up to 6 months post-stent removal or 6 months post-observation of complete distal migration
Number of Patients	Up to 92 patients
Number of Centers	Up to 15 centers globally, including up to 8 centers in the U.S.
Primary Endpoint	<u>Primary Effectiveness Endpoint:</u> Pain Reduction Pain reduction will be assessed at 6 months post-stent removal or 6 months post-observation of complete or partial stent migration compared to pain collected at baseline. Baseline for patients without a plastic pancreatic stent immediately prior to study stent placement will be at the time of enrollment. Baseline for patients with a plastic pancreatic stent immediately prior to study stent placement will be at the time of study stent placement.

	Pain will be scored between 0 and 100 as the mean of the VAS Pain Score and Frequency of Pain sectors of the Izbicki pain scale. Complete pain relief is defined as pain score ≤ 10, and partial pain relief is defined as pain score > 10 and reduced by at least 50% compared to baseline. Complete or partial pain relief in the setting of a 50% higher average daily narcotic dose will be considered a primary effectiveness endpoint failure. Average daily narcotic dosage for prior month will be assessed at baseline visit prior to plastic or study stent placement, whichever is implanted first, and at 6 months post-stent removal/observation of complete distal migration. Patients who experience stent migration in setting of recurring pain (VAS Pain Score of ≥ 20) will be considered as having failed the primary effectiveness endpoint. Patients who are restented in the setting of recurring pain will be considered as having failed both the primary effectiveness endpoint and the secondary endpoint for stricture resolution and may only be restented with a non-study stent. Restenting with a new study stent may only occur during the initial stent placement procedure for such situations as stent misplacement, improper stent size choice, or other conditions, as necessary and will not be considered a primary effectiveness endpoint failure or a secondary endpoint failure for stricture resolution. <u>Primary Safety Endpoint:</u> Rate of related Serious Adverse Events (SAEs) from WallFlex Pancreatic stent placement to end of study. Relatedness will be determined by the PI, reporting if the SAE is related to the study stenting procedure, to the indwelling study stent, to study stent removal and/or to study stent migration. Pain thought to be caused by WallFlex Pancreatic stent expansion will be reported, but will not count towards the endpoint if all three of the following conditions apply:[5] 1. Pain can be managed by medication, with the exception of injectable narcotic use for more than 24 hours. 2. Pain does not cause WallFlex Pancreatic stent removal. 3. Pain resolves by 72 hours after WallFlex Pancreatic stent placement.
Secondary Endpoints	<u>Effectiveness</u> 1. Stricture Resolution

	Stricture resolution will be assessed at the time of stent removal or observation of complete or partial stent migration. Stricture resolution is defined as maintained pain relief without need for restenting or, if pain recurs, confirmation of stent patency adequate for providing drainage of the pancreatic duct. Restenting with a non-study stent will take place if there is no improvement of clinical status (see definition in secondary endpoint 2 below) and associated persistence of the stricture based on imaging. Imaging will be conducted per standard of practice and may be prompted by lack of improved clinical status and may consist of non-invasive imaging or pancreatogram. A pancreatogram will only be performed if an ERCP is necessitated for a reintervention with or without restenting. *NOTE: Patients who are restented for recurring pain (VAS Pain Score of ≥ 20) will be considered a failure for stricture resolution and the primary endpoint and may only be restented with a non-study stent.* *Restenting with a new study stent may only occur during the initial stent placement procedure for such situations as stent misplacement, improper stent size choice, or other conditions, as necessary and will not be considered a secondary effectiveness stricture resolution endpoint failure or a primary endpoint failure.* 2. Improved clinical status compared to baseline assessed at each study visit. Improved clinical status is defined as improvement in at least one and deterioration in none of the following: Pain, Weight and Quality of Life (QOL) • Pain: Scored between 0 and 100 as the mean of the VAS Pain Score and Frequency of Pain sectors of the Izbicki pain scale. • Weight • Quality of life: Recorded using SF12 3. Recurrence of Stricture Stricture recurrence will be assessed in the subset of patients who had stricture resolution at stent removal or observation of complete or partial stent migration. Recurrence of stricture is defined as recurrence of pain with loss of adequate pancreatic duct drainage requiring restenting. Restenting will take place if there is deterioration of clinical status (see definition in secondary endpoint 2 above) and documented recurrent stricture based on imaging. Imaging may be prompted by

	deterioration of clinical status and may consist of non-invasive imaging or of a pancreatogram. A pancreatogram will only be performed if an ERCP is necessitated for a reintervention with or without restenting. 4. Stent Functionality Stent functionality will be assessed from stent placement until stent removal or observation of complete or partial stent migration. Stent functionality is defined as adequate pancreatic duct drainage reflected by reduction of pain and lack of restenting. 5. Izbicki pain scale assessed at each study visit The Izbicki pain scale (see appendix in section 22.1) has four sectors related to severity of pain, frequency of pain, analgesic medication, and disease-related inability to work. 6. Average daily narcotic dose for prior month assessed at each study visit 7. Maintenance of the VAS Pain Score and Frequency of Pain Score recorded at 6 months post-stent removal compared with that recorded at the time of plastic stent removal, for patients with plastic pancreatic stent indwelling immediately prior to study stent placement <u>Technical Success</u> 8. Ability to deploy the stent in satisfactory position (Stent Placement Success). Ease of placement will also be assessed.on a 5 point Likert scale. Satisfactory position is defined as the stent being across the stricture, without visible occluding impaction at the genu of the pancreatic duct and with distal end of the stent visible in the duodenum. 9. Successful endoscopic stent removal (Endoscopic Stent Removal Success). Endoscopic stent removal success is defined as ability to remove stent endoscopically (forceps, snare) without serious stent removal-related adverse events. Ease of removal will also be assessed.on a 5 point Likert scale. Use of stent-in-stent removal technique will be considered a removal failure. For patients who experience complete distal migration of the study stent, this endpoint will not be evaluated. <u>Safety and Device Events</u> 10. Device Events, including findings not associated with adverse

	events, such as but not limited to asymptomatic stent migration.
Study Visits and Follow-Up Schedule	• Baseline Visit: Demographics, Medical History, Symptom Assessment including Pain Score, Concomitant Medications (including injectable narcotics), Average Daily Narcotic Dose, Weight, Quality of Life Score, EPS History, Adverse Events, Imaging (if applicable). If ESWL is deemed necessary at Baseline visit, patient may receive a plastic pancreatic stent placed for 30 to 90 days before study stent placement at the discretion of the Investigator, for example, if there is concern about stone fragments of stone sludge in side branches of the pancreatic duct. • WallFlex Pancreatic Stenting Procedure: Pre-stenting pancreatic stone clearance (if applicable), Pancreatic Duct Imaging or other imaging, WallFlex Pancreatic Stent Placement, EPS (if required), Pain Score (prior to stent procedures), Weight, Concomitant Medications (including injectable narcotics), Average Daily Narcotic Dose, Quality of Life, Adverse Events, Plastic Stent Removal prior to study stent placement, as applicable • Indwell Follow-up via Telephone or in Person on Month 1 and Month 3: Pain Score, Concomitant Medications (including injectable narcotics), Average Daily Narcotic Dose, Weight, Quality of Life Score, Adverse Events • Study Stent Removal(s) intended after 6 months of stent indwell: Pain Score prior to Stent Removal, Concomitant Medications (including injectable narcotics), Average Daily Narcotic Dose, Stent Removal Procedure(s), Weight, Quality of Life Score, Adverse Events, Pancreatic Duct imaging or other imaging to assess stricture resolution • Post-Removal Follow-up via Telephone or in Person 3 months after stent removal or observation of complete distal migraton: Pain Score, Concomitant Medications (including injectable narcotics), Average Daily Narcotic Dose, Weight, Quality of Life Score, Adverse Events • Post-Removal Follow-up via Telephone or in Person 6 months after stent removal or observation of complete distal migraton: Pancreatic Duct Imaging or other Imaging, Pain Score, Concomitant Medications (including injectable narcotics), Average Daily Narcotic Dose, Weight, Quality of Life Score, Adverse Events • OPTIONAL: If a naso-pancreatic drain is placed after stent removal, then repeated pancreatographic assessment of stricture resolution at 24 to 72 hours post stent removal. • Additional visits as needed

Key Inclusion Criteria	1. Age 18 or older 2. Willing and able to comply with study procedures and follow-up schedule and provide written informed consent to participate in study 3. Chronic pancreatitis induced stricture of Cremer Type IV, namely distal dominant stricture with upstream ductal dilation. 4. For patients with a prior plastic pancreatic stent: VAS Pain Score and Frequency of Pain sectors of the Izbicki pain scale at the time of placement of the plastic stent. 5. Availability of narcotic dosage for at least one month prior to baseline visit for patients who do not have a prior plastic pancreatic stent or availability for one month prior to placement of prior plastic pancreatic stent, where applicable. 6. VAS Pain Score of ≥ 20 before study stent placement for patients without a prior plastic pancreatic stent. VAS Pain Score of ≥ 20 before initial plastic pancreatic stent placement for patients with a prior plastic pancreatic stent indwelling for 90 days or less before study stent placement. VAS Pain Score is captured via Izbicki pain scale. 7. Pain occurring weekly or more frequently (assessed by Frequency of Pain sector of the Izbicki pain scale) as reported before study stent placement for patients without a prior plastic pancreatic stent, or before placement of initial plastic pancreatic stent for patients with a prior plastic pancreatic stent indwelling for 90 days or less before study stent placement. 8. Minimum 5 mm diameter of dilated duct immediately upstream of pancreatic duct stricture 9. Prior clearance of pancreatic stones where needed • If pancreatic duct stone clearance prior to placement of the study stent includes ESWL, then a plastic pancreatic stent may be placed immediately after the ESWL procedure at the discretion of the Investigator, for example, if there is concern about stone fragments of stone sludge in side branches of the pancreatic duct, and may be left indwelling for 30-90 days. • If new pancreatic duct stones requiring ESWL have formed by the time of intended study stent placement, then the patient will not receive the study stent and be excluded from the study. Further treatment of the patient will be provided per standard of practice outside of the study. In case the study stent is not placed during the same session in which the plastic stent is removed, the pain score needs to be collected again

	prior to study stent placement. 10. Prior endoscopic pancreatic sphincterotomy (EPS), historically or to be provided at time of SEMS placement as applicable.
Key Exclusion Criteria	1. Pancreatic or peri-ampullary cancer with or without pancreatic duct strictures caused by malignancy 2. Biliary strictures caused by chronic pancreatitis that are symptomatic and/or in need of therapeutic intervention 3. Perforated duct 4. Ansa pancreatica 5. Presence of pancreatic cysts suspected to be cystic tumor or requiring transmural drainage 6. Duodenal/groove pancreatitis 7. Autoimmune pancreatitis 8. Pancreatic duct stenoses not located in the head of the pancreas 9. Failed access during an attempted ERCP on a prior date at the investigational center 10. Duration of indwell of one single plastic pancreatic stent or cumulative duration of consecutive single plastic pancreatic stents immediately prior to study stent placement exceeding 90 days 11. History of prior single pancreatic plastic stent(s) followed by a stent-free period shorter than 1 year before enrollment into the study 12. History of prior side-by-side multiple pancreatic plastic stents up to one year prior to enrollment 13. History of prior pancreatic metal stent(s) 14. Reported recent history of acute relapsing pancreatitis in the absence of chronic pancreatitis 15. Patients for whom endoscopic techniques are contraindicated. 16. Patients who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor 17. Inability or refusal to comply with the follow-up schedule including patients living at such a distance from the investigational center that attending follow-up visits would be unusually difficult or burdensome
Statistical Methods	

Primary Statistical Hypotheses	A literature search was performed on plastic pancreatic stenting in CP. Ten (10) articles that represent 392 evaluable patients[2-11] were found. Primary Effectiveness Endpoint: A meta-analysis of "pain reduction" reported in these articles yielded a point estimate of 66% with a 95% Confidence Interval (CI) of 53% to 76%, using a random effects model. Statistical testing will be conducted to determine if "pain reduction" using the WallFlex Pancreatic Stent is greater than 53%, assuming an observed "pain reduction" rate of 75% and using an exact test with a one-sided alpha of 0.025 and power of 80%, 43 patients will be required. Primary Safety Endpoint: The same literature search as above was used; however, one article, Seza et al. did not report on "related serious adverse events." Therefore, nine (9) articles representing 386 evaluable patients were found. A meta-analysis of "related serious adverse events" reported in these articles yielded a point estimate of 25% with a 95% CI of 19% to 32%, using a random effects model. Statistical testing will be conducted to determine if "related serious adverse events" is less than 32%, assuming an observed "related serious adverse event" rate of 15% and using an exact test with a one-sided alpha of 0.025 and power of 80%, 57 patients will be required. Taking the larger of the two hypotheses and compensating for possible loss of patients after enrollment, an additional 10% of patients will be required, for a total of 64 patients. The percentage of patients who do not meet the inclusion criteria levels of the VAS pain score (≥ 20) and frequency of pain score (50, 75, or 100) at the time of study stent placement, due to a prior single plastic pancreatic stent, is anticipated to range from 20-30%. Therefore, we propose to enroll up to 92 patients so as to have 64 patients who met the inclusion criteria levels of the VAS pain score (≥ 20) and frequency of pain score (50, 75, or 100) at the time of study stent placement.

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1 Introduction

1.1 Literature Review

Chronic pancreatitis (CP) is a debilitating disease. Pain is the principal symptom associated with CP. The cause of pain may be multi-factorial. Correlation between morphological aspects of CP and phenotypical patient presentations including frequency and severity of pain is ill understood. Response to various treatment modalities for the pain – medical management, endotherapy, or surgery – is also poorly predicted. However, it is well recognized that in some patients the pancreatic type pain seems associated with pancreatic duct (PD) obstruction and associated PD dilation. Endotherapy using pancreatic stents may have a beneficial effect in such cases by calibrating the PD strictures, reducing upstream ductal dilation and reducing pain. However, calibaration of PD strictures may not alleviate pain if the origin of the pain has causes other than PD hypertension and dilation. Thus, success of endotherapy using any type of PD stents should combine assessment of pain and calibration of the PD stricture without clinically significant stent-induced ductal changes.

In the treatment of benign PD strictures often in the presence of PD stones caused by CP, the ultimate clinical objective is acceptable quality of life including durable pain control without major complications, preferably stent-free. The gold standard of treatment in this indication remains surgery[1,2]; however, the morbidity associated with these major surgical procedures has made endoscopic, less invasive alternatives a first-line approach for simple benign main PD strictures associated with CP at several expert centers. Endotherapy in this indication mostly consists of single or multiple pancreatic plastic stents[2-11]. The most frequently quoted publication[5] on long-term resolution of refractory PD strictures after temporary indwell of multiple plastic stents in patients with severe CP reports effectiveness comparable to surgical outcomes. A meta-analysis of publications of pancreatic plastic stenting in CP patients[2-11] was used as a basis to generate the hypothesis of the current trial.

Use of self-expanding metal stents (SEMS) in benign main PD strictures associated with painful chronic pancreatitis (CP) was first described in the 1990s, culminating in a recommendation[12] that use of uncovered SEMSs in the PD should be avoided and that use of covered SEMSs (CSEMSs) in the PD holds promise in this indication. Compared to resective or bypass surgery, the use of SEMS is less invasive. Compared to MPS, the use of SEMS is anticipated to result in similar long-term stent-free pain relief, however requiring a shorter duration of stent therapy and fewer ERCPs. Literature-based values are summarized below.

Table 1.1-1: Plastic Stent Literature Values

Study	Number of ERCPs	Total PS indwell duration
Eleftheriadis 2005[2]	Median 3 Range 1-18	Median 23 months Range 2-134 months
Vitale 2004[3]	Mean 4.1	Range 3-12 months
Topazian 2005[4]	Mean 3.2	Intended 6 months, actual duration not reported
Costamagna 2006[5]	Not reported	Mean 7 months Range 5-11 months
Farnbacher 2006[6]	Not reported	Mean 10 months±10 months
Ishiara 2006[7]	Not reported	Mean 335±31 days
Cahen 2007[8]	Median 5 Range 1-11	Mean 27 weeks Range 6-67
Weber 2007[9]	Not reported	Mean 5.6 months Range 1-1- months
Seza 2011[10]	Not reported	Mean 15.2±3.1 months
Gabrielli 2005[11]	Not reported	Not reported

A literature review of 2000-2012 yielded 5 publications with series of 5 or more cases totaling 72 cases[13-17] pertaining to benign PD stricture resolution after treatment using CSEMS. After stent indwell ranging from 2 to 9 months, CSEMS removal was attempted in 71 patients and was achieved without difficulty in 97% (69/71). In 3% (2/71) CSEMS were embedded and required a stent-in-stent technique for subsequent removal. Overall clinical success after post stent removal follow-up ranging from 4 to 20 months averaged 83% (59/71) (range 40%-100%). The overall reintervention rate was 18% (13/72) (range 8%-45%). There were 22 reported stent-related complications in 72 patients, including immediate post FCSEMS placement pain that may require stent removal in some patients.

Of note are publications by the American Society of Gastroenterological Endoscopy (ASGE) and the European Society of Gastroenterological Endoscopy (ESGE) on endotherapy in patients with painful CP:

- In an ASGE Status Evaluation Report in 2013[18], the ASGE states: *"Pancreatic duct stenting can resolve or improve symptoms in chronic pancreatitis patients with pancreatic duct strictures. With pain relief as the endpoint, placement of plastic stents*

*across pancreatic strictures has 70% to 94% short-term and 52% to 80% long-term effectiveness.[58-63] Stenting is usually required for multiple months with frequent stent changes. Fully-covered SEMSs have been used to treat chronic pancreatitis strictures in small uncontrolled studies.[64,65] After placement for 2 to 3 months, the SEMSs were removed with resolution of strictures in all patients and with some improvement in pain. Frequent adverse events of stent migration and stent-induced strictures were reported. In very small case series, plastic or metal stents were placed in the pancreatic duct across a malignant stricture to relieve pain thought to be caused by ductal obstruction. Pain was decreased in 75% to 90% of patients.[66,67]"*and *"The main adverse events of pancreatic stents include migration, stent occlusion, and stent-induced pancreatic ductal changes. Undesired stent migration occurs in 5.2% (proximal) and 7.5% (distal) of cases.[108] Because of the generally smaller diameter stents used in the pancreas, approximately 50% will be occluded by 4 weeks, with the majority occluded by 3 months.[45,46,109,110] Pancreatic ductal changes can occur in as many as 36% to 83% of ducts after stenting for as briefly as 2 to 3 weeks.[111,112] Ductal changes occur more frequently in patients with a normal pancreatogram before stenting and may be permanent in one third of cases. Pancreatitis was reported in 3% with removal of prophylactic pancreatic duct stents even without ERCP.[113]"*

- In an ESGE Guideline in 2012[19], the ESGE states: *"Pancreatic stenting is technically successful in 85–98% of attempted cases[58–60, 64]; it is immediately followed by pain relief in 65–95% of patients[58–61,63–65, 68]; during follow-up (14–58 months), pain relief reported in 32%–68% of patients[25, 37,59–61, 63, 64, 68]."* and *"The ESGE recommends treating dominant MPD stricture by inserting a single 10-Fr plastic stent, with stent exchange planned within 1 year even in asymptomatic patients to prevent complications related to long-standing pancreatic stent occlusion (Recommendation grade C). Simultaneous placement of multiple, side-by-side, pancreatic stents could be applied more extensively, particularly in patients with MPD strictures persisting after 12 months of single plastic stenting. At this time point, the ESGE recommends that available options (e. g., endoscopic placement of multiple simultaneous MPD stents, surgery) be discussed by a multidisciplinary team (Recommendation grade D)."* and "*Patency of pancreatic SEMSs is short with regard to life expectancy of patients with chronic pancreatitis (Evidence level 2–). Preliminary studies suggest that temporary placement of fully covered SEMS is safe and allows resolution of MPD strictures plus pain relief in a majority of patients but no follow-up longer than 1 year is available (Evidence level 2+)."* and "*Uncovered SEMSs should not be inserted in MPD strictures (Recommendation grade D); temporary placement of fully covered SEMSs holds promise but it should be performed only in setting of trials with approval of the institutional review board (Recommendation grade C)."*

1.2 Prior Clinical Trials

In addition to the above publications, preliminary data is available from a small 10 patient trial conducted with the Fully Covered WallFlex Pancreatic Stent. Patients with painful chronic pancreatitis of Cremer Type IV were enrolled between June and September 2014. Intended indwell was 3 months in 5 patients and 6 months in 5 patients. In total 14 stents

were placed, with 2 patients having immediate removal and replacement of the initial stent due to deployment in unsatisfactory position and 2 patients needing a second stent placement after premature complete distal migration of the first indwelling stent. Stent migration without symptoms, thought to be a reflection of adequate calibration of the benign stricture, occurred in 6 stent placements, not requiring restenting. Clinically meaningful complete distal migration (CDM) with symptoms occurred in 25% (3/12) of stent placements with intended stent indwell. There were no proximal stent migrations. Endoscopic stent removal was performed per-protocol easily in one patient after a 3 month indwell and in 2 patients after a 6 month indwell without stent removal-related adverse events (AEs). After a median follow-up of 196 days (range 175 - 373) after stent removal or observation of CDM of the stent, 80% (8/10) of patients remained stent-free. Longer term follow-up is ongoing. One patient had premature CDM followed by placement of plastic stents. One patient had no pain relief after SEMS placement and had subsequent pancreatic diversion surgery which did not provide pain relief either. Serious Adverse events (SAEs) occurred in 50% (5/10) of patients, with 7 SAEs (2 pain associated with premature CDM, 2 transient pain related to stent expansion immediately following stent placement, 1 pain unresolved by stenting or subsequent pancreatic diversion surgery, 1 bacterial infection and 1 mild acute pancreatitis). No SEMS needed to be removed due to intolerable pain after SEMS placement. There were no stent-induced ductal changes.

1.3 Conclusion

These publications and published expert opinions conclude that the use of fully covered SEMSs (FCSEMSs) is feasible and can be safe and effective for treatment of Cremer type IV benign PD strictures caused by CP.

2 Device Use and Description

2.1 Device Description

Study devices are manufactured by Boston Scientific Corporation. The WallFlex™ Pancreatic RX Fully Covered Soft Stent System consists of a flexible delivery system preloaded with a self-expanding pancreatic metal stent. The stent is made from a metallic radiopaque material that is formed into a cylindrical mesh. The stent is offered fully covered with Permalume™ Coating, a translucent silicone polymer, to reduce the potential for ingrowth through the stent. The stent has a retrieval loop for removal during the initial stent placement procedure. The retrieval loop may be used in the event of incorrect placement and/or removal from benign strictures. The stent has a flare on the duodenal end to prevent migration into the pancreas. The WallFlex™ Pancreatic RX Fully Covered Soft Stent System is provided sterile using ethylene oxide and is a single use device.

The study device is not approved for commercial use. However, the clinical study will be conducted only in countries where the WallFlex Pancreatic Stent is approved for the clinical trial indication for use by the Competent Authority (CA). Local EC (Ethics Committee)/IRB (Institutional Review Board) approval will be obtained at each participating center.

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

Table 2.1-1: Clinical UPN (RX, Soft)

	Length	Width	
		6mm	8mm
Rapid Exchange	40 mm	M00577420	M00577480
	50 mm	M00577430	M00577490
	60mm	M00577440	M00577500

For a detailed description of the WallFlex™ Pancreatic RX Fully Covered Soft Stent System, please reference the Investigator's Brochure.

2.2 Device Use

- The WallFlex Pancreatic Stent is intended to facilitate drainage of the pancreatic duct to reduce pain in patients with painful chronic pancreatitis.
- Prior to WallFlex Pancreatic stent placement, the patient must receive/have received an endoscopic pancreatic sphincterotomy (EPS). The EPS can be administered at the time of the stent placement procedure or can have been administered during a prior endoscopic procedure.
- Investigators in this trial should be experienced with pancreatic endotherapy.

3 Primary Objective

To prospectively document the performance of a FCSEMS for treatment of pancreatic duct strictures in patients with painful chronic pancreatitis.

4 Endpoints and Study Design

4.1 Primary Effectiveness Endpoint

Pain Reduction

Pain reduction will be assessed at 6 months post-stent removal or 6 months post-observation of complete or partial stent migration compared to pain collected at baseline. Baseline for patients without a plastic pancreatic stent immediately prior to study stent placement will be at the time of enrollment. Baseline for patients with a plastic pancreatic stent immediately prior to study stent placement will be at the time of study stent placement.

Pain will be scored between 0 and 100 as the mean of the VAS Pain Score and Frequency of Pain sectors of the Izbicki pain scale.

Complete pain relief is defined as pain score ≤ 10, and partial pain relief is defined as pain score > 10 and reduced by at least 50% compared to baseline.

Complete or partial pain relief in the setting of a 50% higher average daily narcotic dose will be considered a primary effectiveness endpoint failure. Average daily narcotic dosage for prior month will be assessed at baseline visit prior to plastic or study stent placement, whichever is implanted first, and at 6 months post-stent removal/observation of complete distal migration.

Patients who experience stent migration in setting of recurring pain (VAS Pain Score of ≥ 20) will be considered as having failed the primary effectiveness endpoint.

Patients who are restented in the setting of recurring pain will be considered as having failed both the primary effectiveness endpoint and the secondary endpoint for stricture resolution and may only be restented with a non-study stent.

Restenting with a new study stent may only occur during the initial stent placement procedure for such situations as stent misplacement, improper stent size choice, or other conditions, as necessary and will not be considered a primary effectiveness endpoint failure or a secondary effectiveness stricture resolution endpoint failure.

4.2 Primary Safety Endpoint

Primary Safety Endpoint:

Rate of related SAEs from WallFlex Pancreatic stent placement to end of study.

Relatedness will be determined by the PI, reporting if the SAE is related to the study stenting procedure, to the indwelling study stent, to study stent removal and/or to study stent migration.

Pain thought to be caused by WallFlex Pancreatic stent expansion will be reported, but will not count towards the endpoint if all three of the following conditions apply:

1. Pain can be managed by medication, with the exception of injectable narcotic use for more than 24 hours.
2. Pain does not cause WallFlex Pancreatic stent removal.
3. Pain resolves by 72 hours after WallFlex Pancreatic stent placement.

4.3 Secondary Endpoints

Effectiveness

1. Stricture Resolution

   Stricture resolution will be assessed at the time of stent removal or observation of complete or partial stent migration.

   Stricture resolution is defined as maintained pain relief without need for restenting or, if pain recurs, confirmation of stent patency adequate for providing drainage of the pancreatic duct.

   Restenting with a non-study stent will take place if there is no improvement of clinical status (see definition in secondary endpoint 2 below) and associated persistence of the

stricture based on imaging. Imaging will be conducted per standard of practice and may be prompted by lack of improved clinical status and may consist of non-invasive imaging or pancreatogram. A pancreatogram will only be performed if an ERCP is necessitated for a reintervention with or without restenting.

NOTE: Patients who are restented for recurring pain (VAS Pain Score of ≥ 20) will be considered a failure for stricture resolution and the primary endpoint and may only be restented with a non-study stent.

Restenting with a new study stent may only occur during the initial stent placement procedure for such situations as stent misplacement, improper stent size choice, or other conditions, as necessary and will not be considered a secondary effectiveness stricture resolution endpoint failure or a primary effectiveness endpoint failure.

2. Improved clinical status compared to baseline assessed at each study visit.

   Improved clinical status is defined as improvement in at least one and deterioration in none of the following: Pain, Weight and Quality of Life (QOL)

   - *Pain: S*cored between 0 and 100 as the mean of the VAS Pain Score and Frequency of Pain sectors of the Izbicki pain scale.
   - *Weight is measured*
   - *Quality of life: Recorded using SF12*

3. Recurrence of Stricture documented by recurrence of pain with loss of adequate pancreatic duct drainage.

   Recurrence of stricture is defined as need for restenting. Restenting will take place if there is deterioration of clinical status (see definition in secondary endpoint 2 above) and documented recurrent stricture based on imaging. Imaging may be prompted by deterioration of clinical status and may consist of non-invasive imaging or of a pancreatogram. A pancreatogram will only be performed if an ERCP is necessitated for a reintervention with or without restenting.

4. Stent Functionality

   Stent functionality will be assessed from stent placement until stent removal or observation of complete or partial stent migration.

   Stent functionality is defined as adequate pancreatic duct drainage reflected by reduction of pain and lack of restenting.

5. Izbicki pain scale assesed at each study visit

   The Izbicki pain scale (see appendix in section 22.1) has four sectors related to severity of pain, frequency of pain, analgesic medication, and disease-related inability to work.

6. Average daily narcotic dose for prior month assessed at each study visit

7. Maintenance of the VAS Pain Score and Frequency of Pain Score recorded at 6 months post-stent removal compared with that recorded at the time of plastic stent removal, for patients with plastic pancreatic stent indwelling immediately prior to study stent placement

Technical Success

8. Ability to deploy the stent in satisfactory position (Stent Placement Success).

   Satisfactory position is defined as the stent being across the stricture, without visible occluding impaction at the genu of the pancreatic duct and with distal end of the stent visible in the duodenum. Ease of placement will also be assessed.on a 5 point Likert scale.

9. Successful endoscopic stent removal (Endoscopic Stent Removal Success).

   Endoscopic stent removal success is defined as ability to remove stent endoscopically (forceps, snare) without serious stent removal-related adverse events. Ease of removal will also be assessed.on a 5 point Likert scale. Use of stent-in-stent removal technique will be considered a removal failure. If stent migration is noted at time of study stent removal, the patient will be excluded from this endpoint's analysis.

Safety and Device Events

10. Device Events, including findings not associated with adverse events, such as but not limited to asymptomatic stent migration.

4.4 Study Design

This study is a prospective, single arm, pre-approval study. Treatment of up to 92 patients will take place at up to 15 clinical centers. Patient who meet all eligibility criteria will receive the WallFlex Pancreatic stent for up to 6 months stent indwell and 6 months follow-up after stent removal.

4.5 Stent Removal

Stent removal will be performed using a rat-tooth forceps to grasp the retrieval loop on the end of the stent. The stent is gently pulled back with the scope to remove. Forceps, grasper, snare or stent-in-stent technique may be utilized for removal.

Stent removal will be planned after 6 months of stent indwell. Early stent removal may be prompted by increased pain that the investigator deems not to be adequately managed with medication.

4.6 Restenting

Restenting with a non-study stent will take place if there is no improvement of clinical status (see definition in secondary endpoint 2) and associated persistence of the stricture based on imaging. Imaging will be conducted per standard of practice. Such may be prompted by lack of improved clinical status and may consist of non-invasive imaging or of a pancreatogram. A pancreatogram will only be performed if an ERCP is necessitated for a reintervention with or without restenting.

Restenting with a new study stent may only occur during the initial stent placement procedure for conditions such as stent misplacement, improper stent size choice, and other conditions, as necessary.

5 Patient Selection

5.1 Inclusion Criteria

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

1. Age 18 or older
2. Willing and able to comply with study procedures and follow-up schedule and provide written informed consent to participate in study
3. Chronic pancreatitis induced stricture of Cremer Type IV, namely distal dominant stricture with upstream ductal dilation.
4. For patients with a prior plastic pancreatic stent: VAS Pain Score and Frequency of Pain sectors of the Izbicki pain scale at the time of placement of the plastic stent.
5. Availability of narcotic dosage for at least one month prior to baseline visit for patients who do not have a prior plastic pancreatic stent or availability for one month prior to placement of prior plastic pancreatic stent, where applicable.
6. VAS Pain Score of ≥ 20 before study stent placement for patients without a prior plastic pancreatic stent. VAS Pain Score of ≥ 20 before initial plastic pancreatic stent placement for patients with a prior plastic pancreatic stent indwelling for 90 days or less before study stent placement. VAS Pain Score is captured via Izbicki pain scale.
7. Pain occurring weekly or more frequently (assessed by Frequency of Pain sector of the Izbicki pain scale) as reported before study stent placement for patients without a prior plastic pancreatic stent, or before placement of initial plastic pancreatic stent for patients with a prior plastic pancreatic stent indwelling for 90 days or less before study stent placement.
8. Minimum 5 mm diameter of dilated duct immediately upstream of pancreatic duct stricture
9. Prior clearance of pancreatic stones where needed
    - If pancreatic duct stone clearance prior to placement of the study stent includes ESWL, then a plastic pancreatic stent may be placed immediately after the ESWL procedure at the discretion of the Investigator, for example, if there is concern about stone fragments of stone sludge in side branches of the pancreatic duct, and may be left indwelling for 30-90 days.
    - If new pancreatic duct stones requiring ESWL have formed by the time of intended study stent placement, then the patient will not receive the study stent and be excluded from the study. Further treatment of the patient will be provided per standard of practice outside of the study. In case the study stent is not placed during the same session in which the plastic stent is removed, the pain score needs to be collected again prior to study stent placement.
10. Prior endoscopic pancreatic sphincterotomy (EPS), historically or to be provided at time of SEMS placement as applicable

5.2 Exclusion Criteria

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

1. Pancreatic or peri-ampullary cancer with or without pancreatic duct strictures caused by malignancy
2. Biliary strictures caused by chronic pancreatitis that are symptomatic and/or in need of therapeutic intervention
3. Perforated duct
4. Ansa pancreatica
5. Presence of pancreatic cysts suspected to be cystic tumor or requiring transmural drainage
6. Duodenal/groove pancreatitis
7. Autoimmune pancreatitis
8. Pancreatic duct stenoses not located in the head of the pancreas
9. Failed access during an attempted ERCP on a prior date at the investigational center
10. Duration of indwell of one single plastic pancreatic stent or cumulative duration of consecutive single plastic pancreatic stents immediately prior to study stent placement exceeding 90 days
11. History of prior single pancreatic plastic stent(s) followed by a stent-free period shorter than 1 year before enrollment into the study
12. History of prior side-by-side multiple pancreatic plastic stents up to one year prior to enrollment
13. History of prior pancreatic metal stent(s)
14. Reported recent history of acute relapsing pancreatitis in the absence of chronic pancreatitis
15. Patients for whom endoscopic techniques are contraindicated.
16. Patients who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor
17. Inability or refusal to comply with the follow-up schedule including patient living at such a distance from the investigational center that attending follow-up visits would be unusually difficult or burdensome

6 Patient Accountability

6.1 Patient Status and Classification

6.1.1 Enrolled Cohort

A patient is considered "enrolled" after signing the study-specific Informed Consent Form (ICF). Patients 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.

6.1.2 Intent-to-Treat Cohort

This cohort (ITT) consists of those "enrolled" patients who meet all inclusion/exclusion criteria. Any adverse events occurring or resulting from a treatment attempt will be collected. Protocol deviations will be collected as necessary. Patients in this cohort will be counted towards the enrollment ceiling, and this cohort will be considered the primary analysis cohort.

6.1.3 Per-Protocol Cohort

The per-protocol cohort is a subset of the ITT patients who receive a study stent(s) and who do not experience major protocol deviations (ICH E9 definitions).

6.2 Enrollment Controls

The risk of over-enrollment is minimized by utilizing a limited number of clinical centers and maintaining close communication with study centers.

6.3 Withdrawal

All patients 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 patient 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 patients permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal include physician discretion, patient choice to withdraw consent, loss to follow-up and death. While study withdrawal is discouraged, patients 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 patient withdrawal must be completed. Additional data may no longer be collected after the point at which a patient 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 patient withdrawal may be used. Withdrawn patients will not be replaced. Patients who withdraw from the study with the study stent in place will be followed per standard of care at the local institution.

6.4 End of Study Action Plan

Patients will have the study device, the WallFlex Pancreatic Stent, implanted temporarily for up to six months. Per section 7.11, a patient will be considered lost to follow-up if the patient remains unresponsive to communication after three documented attempts by study staff. However, for those patients who remain unresponsive to communication while the stent remains in place, additional attempts will be made to request the patient's return for study stent removal. These additional attempts may include increased telephone and written communications and contact with the patient's primary care physician (if this communication is consented to in the Informed Consent Form).

7 Study Methods

7.1 Data Collection

Procedure/Assessment	Screening/ Baseline	Study Stent Placement****	Month 1 (30 ± 5 Days)	Month 3 (90 ± 10 Days)	Month 6 Study Stent Removal (180 ± 15 Days)	Month 3 Post-Removal Follow-up Visit (90± 15 Days)	Month 6 Post-Removal Follow-Up Visit (180 days ± 15 days)
Informed consent form, including informed consent signature date	X						
Demographics and Medical and EPS History	X						
Weight*	X	X	X	X	X	X	X
EPS		X (if required)					
Pre-stenting pancreatic stone clearance (as applicable)	X***	X					
Study Stent Placement		X					
Study Stent Removal					X		
Pancreatic Duct Imaging (may be non-invasive)	X***	X Pre- and Post-Stent Placement			X** Post-Stent Removal		X
Pain Score, Average Daily Narcotic Dose, and QOL Score*	X	X (prior to all stent procedures)	X	X	X (prior to stent removal)	X	X
Adverse Event Assessment	X***	X	X	X	X	X	X
Concomitant Medications, including injectable narcotics	X	X	X	X	X	X	X

* Weight Pain Score and QOL must be assessed at all visits, including any unscheduled visits.
**Window for imaging is ±4 weeks.
***Applicable at Baseline visit for patients who undergo plastic stent placement for ESWL per inclusion criteria 9.
****Study Stent Placement visit may take place on the same day as Screening/Baseline, if deemed appropriate by the treating physician

7.2 Study Candidate Screening

No study-specific testing will be conducted until after the patient 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 patients who are potential study candidates. Patients 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 patient agrees to participate in the study and signs the ICF, the ERCP procedure may demonstrate that the patient is not a suitable candidate for the study.

7.4 Scoring System

7.4.1 Izbicki Scoring System

The Izbicki Pain Scale incorporates four elements: 1) patient self-estimation of intensity of pain using a visual analog scale (VAS), 2) the frequency of pain attacks, 3) analgesic medication usage and 4) the time periods of inability to work. The sum of the rank values divided by four gives the final value of the pain score. See Appendix 22.1 for the Pain Scale.

Patients will be asked to report on the average pain experienced since the prior visit when reporting pain via VAS for the first element of the Izbicki Pain Scale. Patients will be asked to report the average frequency of pain attacks experienced since the prior visit for the second element of the Izbicki Pain Scale. Please see Appendix 22.5 for further guidance on collecting the VAS and frequency of pain attacks information.

Note: For centers with medication types that do not align with section 3 of the Izbicki Pain scale, relevant corresponding medication types may be made available for scoring.

7.4.2 SF-12

The SF-12 (Short Form 12 Item Survey), see Appendix 22.2, is a twelve question survey based off the larger SF-36 scoring system that assesses overall health-related quality of life. The SF-12 is weighted and summed to provide scales for physical and mental health.

7.4.3 Average Daily Narcotic Dosage

Average Daily Narcotic Dose for the previous month will be calculated for all study patients at all study visits. The value for this data point will be expressed in units of morphine milligram equivalents (MME).

Site personnel will collect narcotic use information as part of concomitant medication data collection at each visit. Documentation of all narcotic dosage increases and/or decreases throughout the patient's participation will be very important for the accurate calculation of Average Daily Narcotic Dose.

Site personnel will convert all daily narcotic dosages for the previous month to MME. The daily MME values obtained will be added together and divided by the number of days in the previous month to obtain the Average Daily Narcotic Dose. The Average Daily Narcotic Dose value will be rounded to the nearest whole number, if necessary.

Please see Appendix 22.4 for examples of Average Daily Narcotic Dosage calculations.

7.5 Screening/Baseline – Office/Hospital Visit

- Informed Consent
- Eligibility Criteria Assessment
- Demographics
- Medical and EPS History
- Pain Score
- Concomitant Medications (including injectable narcotics)
- Average Daily Narcotic Dose for Prior Month
- Weight
- Quality of Life
- EPS History
- Plastic Stent Placement, as applicable per inclusion criteria 9
- Imaging, as applicable
- Adverse Event/Device Event Assessment, as applicable

7.6 WallFlex Pancreatic Study Stent Placement – Office/Hospital Visit

- May be performed on the same day as Screening/Baseline visit, if deemed appropriate by the treating physician

7.6.1 Stent Size Selection

- If the upstream dilated pancreatic duct is ≤ 6 mm, a 6 mm diameter WallFlex Pancreatic stent should be placed.
- If the upstream dilated pancreatic duct is > 6 mm, an 8 mm diameter WallFlex Pancreatic stent should be placed.

7.6.2 Assessments

- Pain Score (prior to stent procedures)
- Weight
- Concomitant Medications (including injectable narcotics)
- Average Daily Narcotic Dose for Prior Month

- Quality of Life
- Pancreatic Duct Imaging (pre-and post-procedure)
- EPS (if required, per section 2.2)
- Plastic Stent Removal prior to study stent placement, as applicable
- Study Stent Placement Procedure
- Adverse Event/Device Event Assessment

7.7 Stent Indwell Follow-Up: Month 1 (30 days ± 5 days) and Month 3 (90 days ± 10 days) – Telephone or Office/Hospital Visit

- Pain Score
- Concomitant Medications (including injectable narcotics)
- Average Daily Narcotic Dose for Prior Month
- Weight
- Quality of Life
- Adverse Event/Device Event Assessment

7.8 Study Stent Removal Visit: Month 6 (180 days ± 15 days) – Office/Hospital Visit

- Pain Score (prior to stent removal)
- Concomitant Medications (including injectable narcotics)
- Average Daily Narcotic Dose for Prior Month
- Weight
- Quality of Life
- Study Stent Removal
- Adverse Event/Device Event Assessment
- Pancreatic Duct Imaging
- OPTIONAL: Pancreatogram 24-72 hours post-stent removal, in case a naso-pancreatic drain was left in place after stent removal.

7.9 Post-Stent Removal Follow-Up: Month 3 (90 days±15 days post-removal) – Telephone or Office/Hospital Visit

- Pain Score
- Concomitant Medications (including injectable narcotics)
- Average Daily Narcotic Dose for Prior Month
- Weight
- Quality of Life
- Adverse Event/Device Event Assessment

7.10 Post-Stent Removal Follow-Up: Month 6 (180 days±15 days post-removal) – Telephone or Office/Hospital Visit

- Pain Score
- Concomitant Medications (including injectable narcotics)

- Average Daily Narcotic Dose for Prior Month
- Weight
- Quality of Life
- Adverse Event/Device Event Assessment
- Pancreatic Duct Imaging

7.11 Additional Visits as Required

- Pain Score
- Concomitant Medications (including injectable narcotics)
- Average Daily Narcotic Dose for Prior Month
- Weight
- Quality of life
- Adverse Event/Device Event Assessment
- Pancreatic Duct Imaging, as applicable

7.12 Study Completion

Patients who receive the WallFlex Pancreatic stent will be followed for 6 months after initial stent removal or 6 months after observation of complete distal migration. See Section 4.3 (secondary endpoint bullet #3) for directions regarding restenting of recurrent strictures.

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

7.13 Source Documents

Table 7.133-1: Source Documentation Requirements

Requirement	Disposition
Imaging before and after study stent placement	Retain at center
Imaging after study stent removal	Retain at center
Imaging 6 months after stent removal/observation of complete distal migration	Retain at center

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

8 Statistical Considerations

8.1 Endpoints

8.1.1 Primary Endpoint

Primary Effectiveness Endpoint:

Pain Reduction

Pain reduction will be assessed at 6 months post-stent removal or 6 months post-observation of complete or partial stent migration compared to pain collected at baseline. Baseline for patients without a plastic pancreatic stent immediately prior to study stent placement will be at the time of enrollment. Baseline for patients with a plastic pancreatic stent immediately prior to study stent placement will be at the time of study stent placement.

Pain will be scored between 0 and 100 as the mean of the VAS Pain Score and Frequency of Pain sectors of the Izbicki pain scale.

Complete pain relief is defined as pain score ≤ 10, and partial pain relief is defined as pain score > 10 and reduced by at least 50% compared to baseline.

Complete or partial pain relief in the setting of a 50% higher average daily narcotic dose will be considered a primary effectiveness endpoint failure. Average daily narcotic dosage for prior month will be assessed at baseline visit prior to plastic or study stent placement, whichever is implanted first, and at 6 months post-stent removal/observation of complete distal migration.

Patients who experience stent migration in setting of recurring pain (VAS Pain Score of ≥ 20) will be considered as having failed the primary effectiveness endpoint.

Patients who are restented in the setting of recurring pain will be considered as having failed both the primary effectiveness endpoint and the secondary stricture resolution endpoint and may only be restented with a non-study stent.

Restenting with a new study stent may only occur during the initial stent placement procedure for such situations as stent misplacement, improper stent size choice, or other conditions, as necessary and will not be considered a primary effectiveness endpoint failure or a secondary effectiveness stricture resolution endpoint failure.

For the patients who have a single plastic stent in place for up to 90 days before receiving the study stent, inclusion criteria #6 and #7 will be reassessed immediately prior to the plastic to study stent exchange. Patients who do not meet the inclusion criteria levels of the VAS pain score (≥20) and frequency of pain score (50, 75, or 100) at the time of stent exchange will be excluded from the primary effectiveness endpoint analyses but will be included in the primary safety endpoint analysis and all secondary endpoint analyses. For the patients who meet the inclusion criteria levels, we will use the scores (VAS Pain Score and Frequency of Pain Score) collected immediately prior to the plastic to study stent exchange as their baseline and include them in the primary effectiveness endpoint analyses.

Primary Safety Endpoint:

Rate of related Serious Adverse Events (SAEs) from WallFlex Pancreatic stent placement to end of study.

Relatedness will be determined by the PI, reporting if the SAE is related to the study stenting procedure, to the indwelling study stent, to study stent removal and/or to study stent migration.

Pain thought to be caused by WallFlex Pancreatic stent expansion will be reported, but will not count towards the endpoint if all three of the following conditions apply:[5]

1. Pain can be managed by medication, with the exception of injectable narcotic use for more than 24 hours.
2. Pain does not cause WallFlex Pancreatic stent removal.
3. Pain resolves by 72 hours after WallFlex Pancreatic stent placement.

8.1.2 Hypotheses/Sample Size

Ten (10) articles[2-11] were identified to be reporting on "pain reduction," representing 392 evaluable patients. One of these articles[10] did not report on "related SAE rate"; thus, for this endpoint we used 9 articles[2-9,11], representing 386 evaluable patients. The table below provides by-publication "pain reduction" and "related SAE" rate used to conduct respective meta-analyses.

Meta-analyses were conducted using a random effects model. The sample sizes were calculated using SAS version 9.4.

Table 8.1.2-1: Pain Reduction and Related SAE Rates by Publication

Study	"Pain Reduction"	"Related SAEs"
Eleftheriadis 2005[2]	62% (62/100)	25% (25/100)
Vitale 2004[3]	83% (62/75)	19% (17/89)
Topazian 2005[4]	60% (9/15)	47% (7/15)
Costamagna 2006[5]	84% (16/19)	0% (0/19)
Farnbacher 2006[6]	55% (53/96)	28% (27/96)
Ishiara 2006[7]	78% (7/9)	0% (0/9)
Cahen 2007[8]	32% (6/19)	26% (5/19)
Weber 2007[9]	82% (14/17)	12% (2/17)
Seza 2011[10]	85% (17/20)	N/A
Gabrielli 2005[11]	32% (7/22)	32% (7/22)

Pain reduction

For "pain reduction" the meta-analysis yielded a point estimate of 66% with a 95% Confidence Interval (CI) from 53% to 76%.

Statistical testing will be performed to determine if the probability of "pain reduction" when using the WallFlex Pancreatic Stent is greater than the performance goal (PG) set at 53%, the lower bound of the 95% CI from the meta-analysis above. Hence, the following hypothesis will be tested:

$$\text{Ho: } \pi_1 \leq 53\%$$

$$\text{Ha: } \pi_1 > 53\%$$

where π_1 is the probability of observing "pain reduction".

Assuming that the observed probability is 75%, 43 patients will be required for the above hypothesis, with a one-sided alpha of 0.025 and power of 80%.

The observed probability of pain reduction was set to 75% given that 8 out of 10 patients in a 10 patient pilot study remained stent free at 6 months post-removal. The primary effectiveness endpoint will be assessed in two ways, namely one using last observation carried forward for patients that are missing 6 month pain data and one counting patients with 6 month pain data as failures. A tipping point analysis will be performed to assess the validity of the associated conclusions.

Related SAEs

For "related SAE rate" the meta-analysis yielded a point estimate of 25% with a 95% CI from 19% to 32%.

Statistical testing will be performed to determine if the probability of "related SAE rate" is lower than 32%, the upper bound of the 95% CI of the meta-analysis. Hence, the following hypothesis will be tested:

$$\text{Ho: } \pi_2 \geq 32\%$$

$$\text{Ha: } \pi_2 < 32\%$$

where π_2 is the probability of observing "related SAE rate".

Assuming that the observed probability is 15%, 57 patients will be required for the above hypothesis, with a one-sided alpha of 0.025 and power of 80%.

The observed probability of the related SAE rate was set to 15% given what was observed in a 10 patient pilot study and the resulting mitigation measures put in place to reduce the risk of observed related SAEs per definition of the Primary Safety Endpoint.

The primary safety endpoint will be assessed in two ways, namely one using all related SAEs (excluding pain thought to be caused by stent expansion per Section 4.2) and one using all related SAEs except those termed as pain by the site.

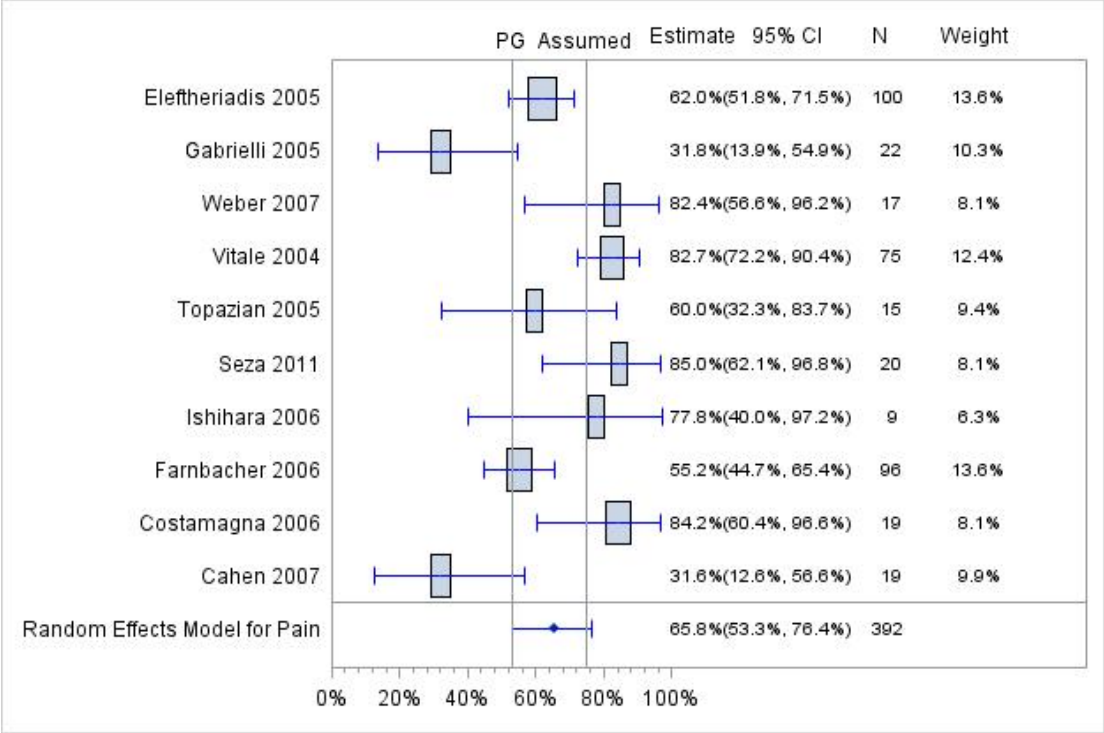
Sample size

Taking the largest of the two sample sizes, namely 43 and 57, and compensating for possible loss of patients after enrollment, an additional 10% of patients will be required, for a total of 64 Intent-to-Treat patients.

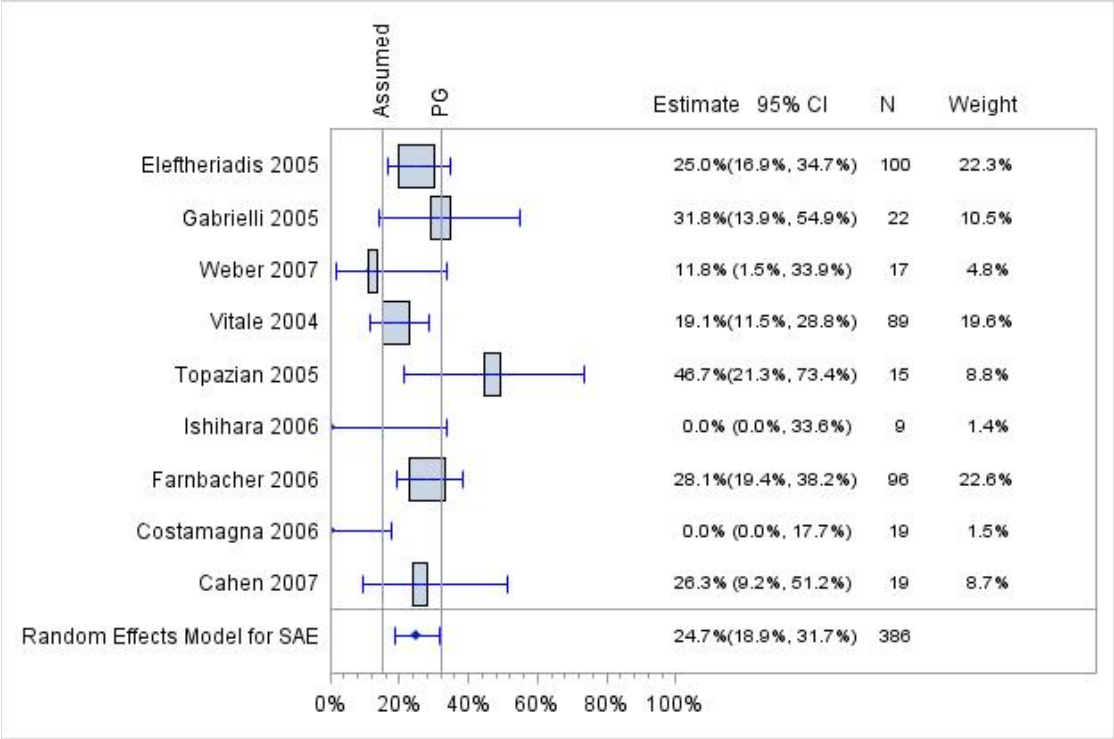
The percentage of patients who do not meet the inclusion criteria levels of the VAS pain score (≥ 20) and frequency of pain score (50, 75, or 100) at the time of study stent placement, due to a prior single plastic pancreatic stent, is anticipated to range from 20-30%. Therefore, we propose to enroll up to 92 patients so as to have 64 patients who met the inclusion criteria levels of the VAS pain score (≥ 20) and frequency of pain score (50, 75, or 100) at the time of study stent placement. No more than 28 subjects who do not meet these inclusion criteria at the time of study stent placement will be enrolled into the study.

Forest plots illustrating the two meta-analyses and marking the selected PG and assumed observed probability are provided below.

Meta-Analysis of Pain



Meta-Analysis of SAE



NOTE: A literature search was performed on metal pancreatic stenting, and 4 articles that represented 61 patients[13-16] were found. The meta-analyses yielded a point estimate of 84% with a 95% CI of (72%, 92%) and 19% with a 95% CI of (8%, 38%) for "pain reduction" and "related serious adverse events," respectively. These are similar to the findings of the meta-analyses for plastic pancreatic stenting.

8.1.3 Sensitivity Analyses

Sensitivity analyses, specifically a tipping-point analysis for the primary endpoint, may be conducted to assess the impact of missing data on interpretation of the results. Missing equals failure method will be used, such that missing data will be added into the primary analyses as failures until the null hypotheses are not rejected any longer. Multiple imputation methods will not be used.

8.2 Statistical Methods

8.2.1 Baseline Data

Patient demographics, medical history, risk factors, pain score, QOL, pancreatic duct imaging, EPS history, and ESWL history will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency statistics for discrete variables.

8.2.2 Post Procedure Data

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical study event schedule and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables.

8.2.3 Subgroup Analyses

The subgroup analyses will include tabulating the primary endpoints and select secondary endpoints by gender. The primary efficacy endpoint will be stratified by narcotic use. (Stratification levels for narcotic use will be based on the data and will not be pre-specified.) Finally, a stratified analysis will be performed to detect potential differences between patients with and without a history of prior side-by-side multiple plastic pancreatic stents. It is not expected that this analysis will be statistically powered to make claims of potential differences between the groups.

8.2.4 Justification of Pooling

The analyses will be performed using data pooled across institutions. An assessment of the poolability of patients across sites will be made by fitting logistic regression models with site as the factor of interest and the primary endpoint as outcomes. Certain baseline variables may also be explored for pooling.

If the P value for the site or baseline variable coefficient is ≥ 0.15, it will be concluded that the treatment effect is not different across sites, and the data can be pooled. If the P value for the site coefficient is <0.15, site differences will be explored.

8.2.5 Mulitvariate Analyses

Univariate and multivariate analyses may be performed to assess the effect of potential predictors on the primary endpoint using logistic regression.

Variables from the following categories will be considered as possible predictors: demographics and medical history. Factors will be modeled multivariately using a stepwise procedure in a logistic regression model. The significance thresholds for entry and exit into the model will be set to $p \leq 0.10$.

8.2.6 Interim Analyses

No formal interim analyses are planned for this study.

8.2.7 Statistical Software

All statistical analyses will be done using The SAS System software, version 8 or higher (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

8.2.8 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior will be documented in an amended Statistical Analysis Plan.

9 Data Management

9.1 Data Collection, Processing, and Review

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

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

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

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the 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 Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study patients 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 local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

10 Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the patient 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 patient in an emergency. 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 patient in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

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

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

12 Device/Equipment Accountability

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. Records shall also be kept by study personnel to document the physical location and conditions of storage of all investigational devices/equipment.

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

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

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 investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the patient.

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 patient 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).
- 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 monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a patient during and after a patient's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the patient of the nature and possible cause of any adverse events experienced.
- Inform the patient of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the patient 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 patient is enrolled in this clinical study.
- Ensure that, if appropriate, patients 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 patient's approval or when required by national regulations, the patient's personal physician about the patient's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a patient's premature withdrawal from clinical investigation while fully respecting the patient's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

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 investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

13.3 Institutional Review Board/ Ethics Committee

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

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

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

13.4 Sponsor Responsibilities

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

Boston Scientific will keep patient's health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use patient's health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to patients; patient 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 patients 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 Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

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

15 Potential Risks and Benefits

15.1 Anticipated Adverse Device Effects

The following anticipated adverse events (AE) have been identified for this study associated with the placement and removal of the study device.

- Pain
- Cholestasis
- Cholangitis
- Pancreatitis
- Secondary stricture formation
- Obstructive Jaundice
- Vomiting
- Bleeding
- Infection
- Sepsis
- Abscess Formation
- Hyperplastic Tissue Reaction
- Tissue trauma (including events such as duct injury, rupture, edema, inflammation, impaction, laceration and necrosis)
- Pancreatic Duct Rupture
- Allergic Reaction
- Pseudocyst development
- Fever
- Death (excluding disease progression)
- Impaction to pancreatic duct wall
- Perforation with or without pneumoperitoneum
- Pseudoaneurysm

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

15.2 Risks Associated with Clinical Trial Participation

Participation in the trial may be demanding and time consuming,

15.3 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 patient selection criteria, close monitoring of the patient's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

15.4 Anticipated Benefits

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

15.5 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 patients is required as outlined in the protocol.

16 Safety Reporting

16.1 Definitions and Classification

Adverse event definitions are provided in Table 16.1-1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 (2015).

Table 16.1-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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 14155-2011*	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

Table 16.1-1: Safety Definitions

Term	Definition
Ref: MEDDEV 2.7/3 (2015)	implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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. **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 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	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.

Table 16.1-1: Safety Definitions

Term	Definition

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

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 16.1-1 for AE definitions).

Any related AE experienced by the study patient after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF. Unrelated AEs will not be collected for this study.

Refer to Section 15 for the known risks associated with the study device(s).

16.2 Relationship to Study Device(s)

The Investigator must assess the relationship of any SAE or AE to the study device, study stent placement procedure, study sent removal and complete distal stent migration. See criteria in Table 16.2-1:

Table 16.2-1: 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 reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Table 16.2-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

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

16.3 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 16.3-1.

Table 16.3-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline (Pre-Market Studies)** (MEDDEV 2.7/3 (2015): 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
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 (unidentified) 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
	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

Table 16.3-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline (Pre-Market Studies)** (MEDDEV 2.7/3 (2015): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
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

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.

16.4 Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use 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 patient'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 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.

16.5 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.

16.6 Adverse Event Coding

MedDRA version 17.1 or higher will be utilized to map verbatim AE terms to medical dictionary-derived terms.

17 Informed Consent

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

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the center'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 center's IRB/EC. Any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the patient and if needed, BSC will assist the center 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:

- 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 patient's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of patients to participate,
- not waive or appear to waive patient's legal rights,
- use native language that is non-technical and understandable to the patient or his/her legal representative,
- provide ample time for the patient to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing patients throughout the clinical study.

The ICF shall always be signed and personally dated by the patient or legal representative and by the investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the patient 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 center 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 patient consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a patient's future health and medical care, that information shall be provided to the affected patient(s) in written form via a revised ICF or, in some situations, enrolled patients 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 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. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the patient population to be re-consented.

18 Suspension or Termination

18.1 Premature Termination of the Study

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

18.1.1 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 patients 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.

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

Any investigator, or IRB/ EC in the study may discontinue participation in the study or withdrawal 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.

18.3 Requirements for Documentation and Patient 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 and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled patient will be managed thereafter will be provided.

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

18.4 Criteria for Suspending/Terminating a Study Center

Boston Scientific Corporation reserves the right to stop the inclusion of patients at a study center at any time after the study initiation visit if no patients 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 patients. The IRB/EC and regulatory authorities, as applicable, should be notified. All patients 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.

19 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 Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

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

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21 Abbreviations and Definitions

Acronym	Definition
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific Corporation
CP	Chronic Pancreatitis
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Resource Organization
CSEMS	Covered Self-Expanding Metal Stent
CT	Computed Tomography
DFU	Directions for Use
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
EPS	Endoscopic Pancreatic Sphincterotomy
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESWL	Extracorporeal Shock Wave Lithotripsy
FCSEMS	Fully Covered Self-Expanding Metal Stent
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISO	International Standards Organization
ITT	Intent-to-Treat
LFT	Liver Function Test
MRCP	Magnetic Resonance Cholangiopancreatography
MS	Metal Stent
PD	Pancreatic Duct
PG	Performance Goal
PI	Principal Investigator
PS	Plastic Stent
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SEMS	Self-Expanding Metal Stent
VAS	Visual Analog Scale

22 Appendices

22.1 Izbicki Pain Scale

	Points
Frequency of pain attacks	
Daily	100
Several times a week	75
Several times a month	50
Several times a year	25
None	0
VAS	
No pain — Imaginative maximum of pain	
0 points — 100 points	
Analgesic medication[a] (morphine-related analgesic potency)	
Morphine	100
Buprenorphine	80
Pethidine	20
Tramaldol	15
Metamizole	3
Acetylsalicylacid	1
Time of disease-related inability to work	
Permanent	100
≤1 year	75
≤1 month	50
≤1 week	25
No inability to work during the last year	0

22.2 SF12

Your Health and Well-Being

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

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

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

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

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

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

22.2 SF12 (continued)

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

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

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

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

22.2 SF12 (continued)

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

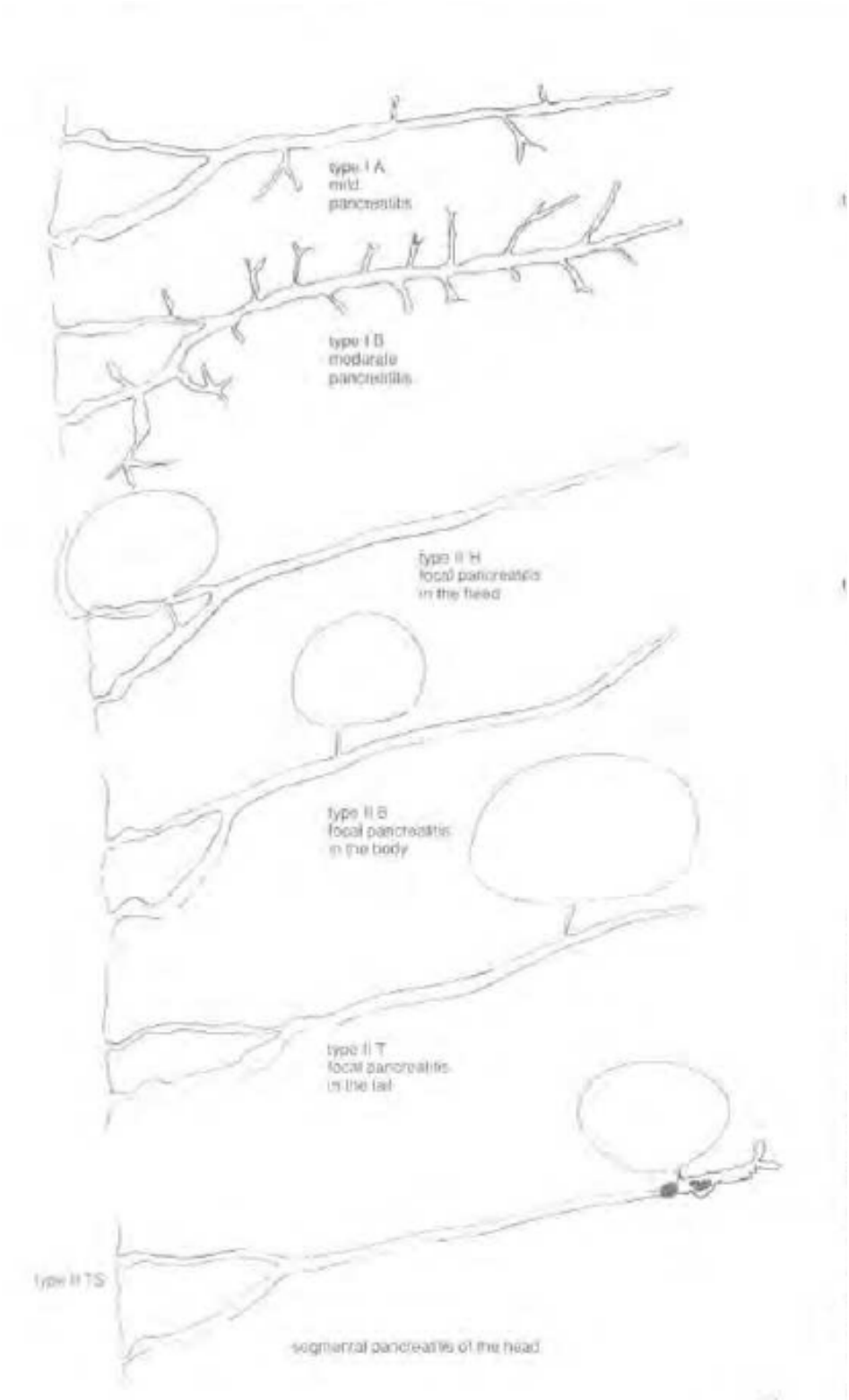
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

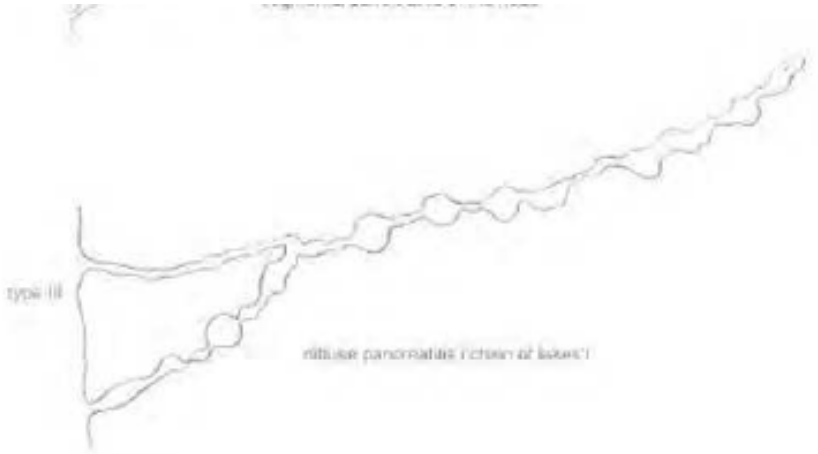
All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

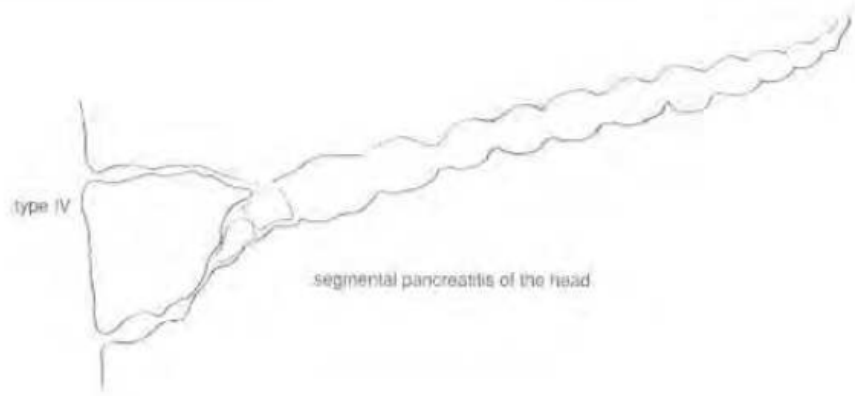
Thank you for completing these questions!

22.3 Cremer Classification of Chronic Pancreatitis



22.3 Cremer Classification of Chronic Pancreatitis (continued)





22.4 Morphine Milligram Equivalent (MME) Narcotic Conversion Guidance

Average Daily Narcotic Dose for the previous month will be calculated for all study patients at all study visits. The value for this data point will be expressed in units of morphine milligram equivalents (MME).

Please see the examples below and the guidance on the following pages for assistance with calculating Average Daily Narcotic Dose.

Example 1:

A patient reporting for a study visit on November 3rd reports to have taken 20 mg/day of Oxymorphone for the previous month.

The MME conversion factor for Oxymorphone is 3.

20 mg/day x 3 MME = 60 MME

Since the patient's daily narcotic dose was constant over the previous month, you can multiply the daily narcotic dose by the MME conversion factor to obtain the Average Daily Narcotic Dose. The Average Daily Narcotic Dose is **60 MME**.

Example 2:

A patient reporting for a study visit on May 11th reports a reduction of Oxycodone from 30 mg/day to 20 mg/day on April 18th of the previous month.

The previous month (April 11th – May 10th) contained 30 days. The MME conversion factor for Oxycodone is 1.5.

Since the patient had two different daily narcotic doses during the previous month, you will have to find the cumulative MME for each time period containing a unique daily narcotic dose then add the cumulative MMEs together and divide the total by the number of days in the previous month. This will provide the Average Daily Narcotic Dose.

For 7 days (April 11th – April 17th), the patient took 30 mg/day of Oxycodone.

7 days x (30 mg/day x 1.5 MME) = 7 days x 45 MME = 315 MME

For 23 days (April 18th – May 10th), the patient took 20 mg/day of Oxycodone.

23 days x (20 mg/day x 1.5 MME) = 23 days x 30 MME = 690 MME

Add the cumulative MMEs together and divide by 30 days:

(315 MME + 690 MME) ÷ 30 days = 1005 MME ÷ 30 days = 33.5 MME

The Average Daily Narcotic Dosage value will be rounded to the nearest whole number, resulting in a final value of **34 MME**.

22.5 Guidance on Collecting VAS Pain Score and Frequency of Pain Attacks Information

The Izbicki Pain Scale incorporates the following four elements in its measurement of pain:

1) patient self-estimation of intensity of pain using a visual analog scale (VAS)

2) the frequency of pain attacks

3) analgesic medication usage

4) the time of disease-related inability to work

The sum of the rank values divided by four gives the final value of the pain score. Please see Appendix 22.1 for more information. The Izbicki Pain Scale will be collected at every study visit. The information below will serve as guidance when collecting information for the first two elements of the Izbicki Pain Scale.

When reporting pain via VAS for the first element of the Izbicki Pain Scale, patients will be asked to report on the average pain experienced since the prior study visit. For the second element of the Izbicki Pain Scale, patients will be asked to report the average frequency of pain attacks experienced since the prior study visit. The manner in which these two questions are posed will depend upon the patient's pain pattern.

What is the patient's pain pattern?

Short and relapsing episodes of pain separated by periods of pain remission	Prolonged periods of fairly constant pain	Unknown or indistinguishable pattern of pain
1st Study Visit Within the previous three months, how strong was your most severe bout of pain? **&** Within the previous three months, how frequently did you experience a bout of pain?	**1st Study Visit** Within the previous three months, how would you score the average level of pain you experienced? **&** Within the previous three months, how frequently have prolonged periods of pain occurred?	**1st Study Visit** Within the previous three months, how would you score your pain? **&** Within the previous three months, how frequently have you experienced pain?
Follow-up Study Visit Since the last study visit, how strong was your most severe bout of pain? **&** Since the last study visit, how frequently did you experience a bout of pain?	**Follow-up Study Visit** Since the last study visit, how would you score the average level of pain you experienced? **&** Since the last study visit, how frequently did prolonged periods of pain occur?	**Follow-up Study Visit** Since the last study visit, how would you score your pain? **&** Since the last study visit, how frequently have you experienced pain?