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Soft Self-expanding Metal Stent to Treat Painful Pancreatic Duct Strictures Secondary to Chronic Pancreatitis: A Prospective Multicenter Trial

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ABSTRACT

Background & Aims Fully covered self-expanding metal stents (FCSEMS) may offer a treatment option for pain associated with a dilated pancreatic duct (PD) in chronic pancreatitis (CP), but optimal patient selection, FCSEMS design, efficacy and safety remain uncertain. We studied an investigational pancreatic FCSEMS for treatment of CP-associated pain.

Methods Patients with painful CP, a dominant distal PD stricture and PD dilation upstream enrolled in a prospective multicenter single-arm trial studying 6-month indwell of a 4-6 cm long, soft pancreatic FCSEMS. Primary efficacy and safety endpoints were pain reduction 6 months after FCSEMS indwell (performance goal $\geq 53\%$) and PD stenting-related serious adverse events (SAEs) respectively (performance goal $< 32\%$). The primary efficacy endpoint was to be assessed in patients with sufficiently severe and frequent pain at FCSEMS placement as a first stent or in exchange of a plastic stent.

Results: Among 67 patients (mean age 52.7 ± 12.5 years, mean time since CP diagnosis 6.4 ± 6.4 years), 34 (50.7%) had plastic stent placement within 90 days of FCSEMS placement, and 46 patients were eligible for the primary efficacy endpoint analysis. Technical success was 97.0% (65/67). The observed primary efficacy (26.1%, 12/46 patients) and safety (31.3%, 21/67 patients) endpoints failed to meet the a priori study hypotheses. Study stent migration occurred in 47.7% (31/65) patients.

Conclusions: Six-month treatment with an FCSEMS did not lead to an expected degree of pain reduction, and migrations and SAEs were common. Further study is needed to clarify optimal decompressive strategy, FCSEMS design and patient selection.

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INTRODUCTION

Abdominal pain is the most common symptom of chronic pancreatitis (CP), observed as the initial presentation in approximately 75% of patients and present during the clinical course of disease in 85%–97%.¹ CP-associated pain is thought to be caused by parenchymal and ductal hypertension and parenchymal inflammation, but the pathogenesis is multifactorial and complex.² For example, pain may be associated with pancreatic duct (PD) dilation and impaired drainage due to strictures or stones; however, pain can occur in the absence of PD dilation, and may not resolve after stone removal and ductal decompression.³ Clinical decision-making for CP is complex, and the implementation of endotherapy, extracorporeal shock wave lithotripsy (ESWL), surgical and medical treatment varies among specialists.⁴ A 2021 systematic review of randomized clinical trials (RCTs) comparing endoscopic therapy versus surgery for the treatment of CP in adult patients with dilation in the main PD concluded that surgical interventions showed superior results when compared to endotherapy in terms of complete long-term pain relief.⁵ However, not all patients are agreeable to or fit for surgery and effective nonsurgical options need to continue to be evaluated and developed. For example, patients with obstructive stones may be offered ESWL alone without any endoscopic or surgical intervention as a first therapeutic approach,⁶ illustrating the fact that morphological selection is important.

The 2020 American College of Gastroenterology Guideline for diagnosis and management of CP recommended surgical intervention over endoscopic therapy in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to PD drainage have been exhausted or unsuccessful.⁷ Endoscopic decompressive procedures include endoscopic retrograde cholangiopancreatography (ERCP) with pancreatic sphincterotomy, stone clearance

(including pancreatoscopy-guided lithotripsy^{8,9}), stricture dilation, and PD stenting, as well as interventional endoscopic ultrasound procedures for placement of a transluminal stent to allow for PD decompression.⁷ Plastic stents have been used for this indication since the early 1990s,¹⁰ while fully covered self-expanding metal stents (FCSEMS) have been studied more recently. A 2021 retrospective study of 80 CP patients reported that in comparison with plastic stents, FCSEMS placement for persistent main PD strictures had favorable long-term clinical efficacy, with its typical complications like spontaneous migration and de novo strictures.¹¹ Similarly, a 2021 meta-analysis concluded “FCSEMS are comparable to multiple plastic stents in the treatment of symptomatic refractory PD strictures. However, use of FCSEMS is associated with increased risk of adverse events”.¹² Three-month use of a modified flared FCSEMS was associated with frequent migration and de novo PD strictures.^{13,14} Subsequently, a modified, nonflared, short fully covered metal stent was developed for treatment of refractory benign PD strictures.¹⁵ Among 27 patients in whom this FCSEMS was successfully placed through the major (n=27) or minor (n=5) duodenal papilla, all achieved pain relief and stricture resolution without stent migration by the time of FCSEMS removal at 3 months after placement, with 5 patients showing asymptomatic de novo focal PD strictures on pancreatograms obtained at that time.¹⁵

To further investigate treatment for PD strictures in patients with painful CP, we conducted a prospective, single-arm trial to test the efficacy and safety of 6-month treatment using a new “soft” FCSEMS. The study was conducted under an Investigational Device Exemption (IDE) protocol approved by the US Food and Drug Administration and Competent Authorities of other participating countries. The IDE protocol provided detailed and stringent definitions of primary

effectiveness and safety endpoints, both of which were failed in the study. A post-hoc analysis aimed to suggest potential future study designs.

METHODS

Study design

We conducted a prospective, multicenter, single-arm clinical trial to evaluate the safety and efficacy of the WallFlex™ Pancreatic RX Fully Covered Soft Stent System (Boston Scientific Corporation, Marlborough, Massachusetts) (**Figure 1**) to treat PD strictures in adults with painful CP (US Food and Drug Administration IDE#: G150185; NCT02802020). After pretesting with a plastic stent and pancreatic stone clearance if needed, the FCSEMS was placed with intended implantation for 6 months. FCSEMS were available in 6-mm or 8-mm diameter and 4-cm, 5-cm, or 6-cm length. After 6-month indwell, the FCSEMS was removed. Patients were observed for an additional 6 months after stent removal or after observation of complete distal (outward) migration (CDM).

Patient population

Eligible patients were adults aged 18 years or older with a CP-induced Cremer Type IV stricture¹⁶ (distal dominant stricture with upstream ductal dilation) and upstream PD ≥ 5 mm in diameter, endoscopic pancreatic sphincterotomy in the past or at study baseline, and pain occurring at least weekly and rated ≥ 20 on the Visual Analog Scale (VAS) Pain Score (1-100 scale¹⁷) at study baseline, i.e. at time of FCSEMS placement for stenting treatment-naïve patients or at time of initial stent placement for patients with a prior plastic pancreatic stent. Prior clearance of PD stones was performed where applicable. If PD stone clearance prior to placement of the study stent included ESWL, then a plastic pancreatic stent could be placed

immediately after ESWL at the discretion of the investigator. However, if new PD stones requiring ESWL subsequently formed before the intended FCSEMS placement, the patient was excluded from the study to be treated per standard of practice outside of the study. Other exclusion criteria were pancreatic or periampullary cancer with or without associated PD strictures, biliary strictures caused by CP and requiring treatment, perforated duct, Ansa pancreatica, pancreatic cysts, duodenal/groove pancreatitis, autoimmune pancreatitis, PD stenoses not located in the head of the pancreas, prior failed access during an attempted ERCP, cumulative plastic pancreatic stent indwell exceeding 90 days within 1 year before enrollment into the study, prior pancreatic metal stent(s), recent acute relapsing pancreatitis, contraindication to endoscopic techniques, inability to comply with study follow-up, or enrollment in another investigational study that would directly interfere with the current study.

All investigational sites obtained approval from their local Institutional Review Boards (IRBs) prior to recruitment of participants for the study. The study was registered in the ClinicalTrials.gov database on June 16, 2016 and was conducted under a US FDA-approved protocol. Competent Authorities in other participating countries also approved the protocol. All enrolled patients provided written informed consent for their procedures and for participation in the study. All authors had access to the study data and reviewed and approved the final manuscript. The study was sponsored by the manufacturer of the FCSEMS used in this study.

Study visits

Baseline screening visit

A screening assessment was performed to document study eligibility, informed consent, baseline demographics, medical and procedural history including prior endoscopic pancreatic sphincterotomy, prior plastic stenting, and prior PD stone clearance.

Pancreatic study stent placement

Pancreatic study stent placement could be performed on the same day as screening at the discretion of the treating physician, or in a separate visit soon afterwards. Investigators were advised to place a 6-mm diameter study stent if the upstream dilated PD was ≤ 6 mm, and an 8-mm diameter study stent if the dilated PD was > 6 mm. Technical success was defined as successful placement of the stent across the intended stricture confirmed on endoscopy and fluoroscopy.

Longitudinal assessments during stent indwell and stent removal

The following assessments were performed at baseline and longitudinally in follow-up visits at 1 month, 3 months and 6 months (stent removal visit): weight, concomitant medications (including injectable narcotics), average daily narcotic dose for prior month, SF-12 quality of life (QOL) score, Izbicki pain score,¹⁸ PD imaging (pre-and post-procedure). Adverse event/device event assessment was conducted as occurring. After stent removal at 6 months, placement of a nasopancreatic drain was optional, followed by pancreatographic assessment of the PD stricture 24-72 hours after study stent removal.

Post-stent removal visits

Follow-up visits were performed 3 months and 6 months after FCSEMS removal or observation of CDM. The final visit 6 months after stent removal included PD imaging.

Study endpoints

Primary efficacy endpoint – Pain reduction

The self-reported pain score (0–100) was the mean of the Visual Analogue Scale (VAS) and Izbicki Frequency of Pain subscore (sum treated as a continuous variable). The remaining 2 components of the full Izbicki pain score system¹⁸ were not used because they were unsuitable for our cohort, i.e. the Izbicki analgetic medication component did not include all medications taken by our patients, and the inability-to-work component included duration > 6 months that could not be assessed in our 6-month study. The primary efficacy endpoint was the proportion of patients who had complete (pain score ≤ 10) or partial (pain score > 10 but reduced at least 50% compared to pain as baseline) pain relief by 6 months after FCSEMS removal or observation of CDM or partial stent migration.

Primary efficacy endpoint failure included any of the following: 1) no pain relief, 2) complete or partial pain relief in the setting of a 50% higher average daily narcotic dose compared to the patient's daily average narcotic dose in the month prior to baseline and at 6 months post-stent removal/observation of CDM, 3) stent migration in setting of recurring pain (VAS Pain Score of ≥ 20), 4) restenting in the setting of recurring pain. Patients were excluded from the intention to treat (ITT) analysis of the primary pain endpoint for insufficient pain level after plastic stent placement (which precluded accurate assessment of study FCSEMS efficacy) or nonevaluable

status due to death or loss to follow-up.

Primary safety endpoint– Rate of related SAEs

The primary safety endpoint was the rate of serious adverse events (SAEs) related to the FCSEMS or study procedures from FCSEMS placement to end of study follow-up. Pain thought to be caused by FCSEMS pancreatic stent expansion was reported, but did not count towards the endpoint if all three of the following conditions applied¹⁹:

1. Pain managed by medication, with the exception of injectable narcotic use for more than 24 hours.
2. Pain not causing pancreatic FCSEMS removal.
3. Pain resolved by 72 hours after pancreatic FCSEMS placement.

Secondary endpoints

The secondary efficacy endpoints were technical success, stent migrations, restenting after removal of FCSEMS or observation of CDM, and change in weight and self-reported QOL, assessed at each visit.

Statistical analysis

Sample size calculation

A literature search on plastic pancreatic stenting in CP yielded ten articles reporting on pain reduction representing a total of 392 evaluable patients¹⁹⁻²⁸. A meta-analysis yielded a point estimate of 66% (95% Confidence Interval (CI), 53%–76%) for the proportion of patients who satisfied pre-defined pain relief success. Based on the meta-analysis findings, we hypothesized that “pain reduction” (as defined in Study endpoints above) would be achieved in a performance

goal of at least 53% of patients receiving the study SEMS. Assuming an observed pain reduction rate of 75% and using an exact test with a one-sided alpha of 0.025, 43 patients were required to obtain power of at least 80%.

Using the same literature search, 9 articles representing 386 patients^{19-26,28} reported on the rate of device-or procedure-related SAEs. This meta-analysis yielded a point estimate of 25% (95% CI, 19%–32%). Therefore, we hypothesized that the proportion of patients reporting one or more related SAE(s) would be below a performance goal of 32%. Assuming an observed SAE rate of 15% and using an exact test with one-sided alpha of 0.025, 57 patients were required to obtain power of at least 80%. Taking the larger of the two sample size calculations and adding 10% for attrition, 64 patients would be enrolled. In addition, we estimated that 20-30% of patients would not meet the pain requirement for a-priori primary efficacy endpoint hypothesis testing at FCSEMS placement in cases of prior plastic stenting. Thus, a maximum of 92 patients could be enrolled.

Statistical analysis

Continuous variables were analyzed using means and standard deviations or median and ranges. Binary variables were reported as frequencies. Primary endpoints were tested using Fisher's exact test, where a *P* value less than 0.025 meant the performance goal was met. All analyses were performed using SAS version 9.4.

RESULTS

Baseline patient and stent placement procedural characteristics

Of 93 patients screened for study eligibility (**Figure 2**), 65 were from US sites, 10 from Belgium, 7 from India, 7 from Italy, 2 from The Netherlands, and 2 from Canada. Sixty-seven eligible patients were enrolled between January 2017 and August of 2020, with a mean age of 52.7 ± 12.5 years. The mean time since first CP diagnosis was 6.4 ± 6.4 years (**Figure 2, Table 1**). Thirty-four patients had prior plastic stent placement within 90 days of study entry.

Thirty (44.8%) FCSEMS placements were on inpatients, with median total hospital stay of 2.0 (range 1.0, 7.0) days (**Table 2**). The FCSEMS was placed through the major papilla in most cases (71.2%, 47/66). Sixty-seven (100.0%) patients had a pancreatic sphincterotomy at some point, including 12 performed during the study stent placement. Forty (59.7%) patients had a biliary sphincterotomy at some point, including 6 performed during the study stent placement. A plastic biliary stent was placed in one case. Most patients had normal PD anatomy (61.2%, 41/67) and 17 (25.4%) had Pancreas divisum (**Figure 3**). Forty-seven patients had other endoscopic procedures performed at the time of FCSEMS placement, including balloon sweep in 31 (46.3%), and pancreatic stone extraction in 27 (40.3%).

Primary efficacy endpoint

Twenty-one of 67 patients were excluded from the ITT analysis of the primary pain endpoint due to insufficient pain level after plastic stent placement, death or loss to follow-up (**Figure 2**).

Among the 46 patients who were eligible for the primary efficacy endpoint ITT analysis of the efficacy hypothesis of the study, 12 (26.1%) achieved complete or partial pain relief by 6 months after FCSEMS removal or observation of CDM, and had less than a 50% increase in narcotic dose. This result did not meet the performance goal of 53.0% ($P = 0.999$) (**Table 3**).

Primary safety endpoint

The overall SAE rate did not meet the safety performance goal ($P=0.513$) (**Table 3**). FCSEMS- or procedure-related SAEs occurred in 21 (31.3%) patients (**Table 4**). Pain was the most commonly reported SAE (14.9%, 10/67 patients), followed by post-ERCP pancreatitis (11.9%, 8/67), CP exacerbation (4.5%, 3/67) and other (4.5%, 3/67) (**Table 4**). One patient had a study stent placed after significant acute on chronic inflammatory changes had improved with prolonged non-stimulatory feeding. Shortly after placement she developed cholestatic liver enzymes and bile duct dilation that improved after a biliary sphincterotomy with the study stent left in place. She subsequently developed acute on chronic pancreatitis complicated by fluid collections and mesenteric vein thromboses requiring hospital admissions. She completed a scheduled stent removal as an outpatient. Two weeks later she was emergently admitted from home to a local hospital but succumbed to overwhelming sepsis and multi-organ failure. Post-mortem study revealed abdominal sepsis as her cause of death.

Secondary endpoints

Technical success

Technical success of FCSEMS placement was attained in 65 (97.0%). FCSEMS sizes (diameter x length) were 6mm x 4cm in 26 (40.0%), 6mm x 6cm in 19 (29.2%), 6mm x 5cm in 8 (12.3%), 8mm x 6cm in 6 (9.2%), 8mm x 4cm in 5 (7.7%), and 8mm x 5cm in one (1.5%) patient. Of the remaining two patients, one had an aborted ERCP after failed cannulation and died of an unknown cause on day 57. In the second, the FCSEMS dislodged after attempted insertion through a tight stricture; instead, 2 plastic stents were placed and removed after 42 days. At 42

days, one prophylactic plastic stent was placed but pain never resolved, and the patient exited the study 6 months after the initial FCSEMS placement attempt.

At intended FCSEMS removal, 38 (58.5%) underwent endoscopic stent removal and 28 (43.1%) were observed to have undergone CDM. All FCSEMS removals and CDMs were uneventful.

Stent migrations

Stent migration was observed in 31 (47.7% of 65) patients, including 28 CDM (**Table 4**), one partial distal migration and 2 proximal migrations. CDMs were uneventful with all migrated FCSEMS spontaneously passing. Of 28 CDM, 11 were asymptomatic, not associated with recurrence of pain, and observed at the time of intended endoscopic FCSEMS removal.

Restenting

Eleven patients had restenting during study follow-up: 7 at the time of FCSEMS removal or observation of CDM, and one each at 6, 8, 13 and 114 days after FCSEMS removal or observation of CDM. Most restenting procedures occurred within 14 days of the FCSEMS removal or observation of CDM.

Secondary strictures

Secondary strictures located at the intraductal edge of the FCSEMS were reported in 5 patients at the time of stent removal or observation of CDM. All five were restented with a single plastic pancreatic stent. Of these, three were restented for less than a month for maintenance of PD drainage or PD stones, one was restented for 63 days, and one exited the study with the plastic stent in place. At the end of follow-up, the latter two cases reported no pain.

Weight and quality of life

Twenty-four (39.3% of 61) patients were reported to have weight gain by 6 months after FCSEMS removal or observation of CDM, with a mean weight change compared to baseline of 1.3 ± 6.9 kg (range -16.2–19.0 kg).

Self-reported QOL score was reported as improved compared to baseline in 71.7% (43/60) of patients by 6 months after FCSEMS removal or observation of CDM. Median change in QOL score increased to +16.4 (range -46.0–79.3) at 6 months.

DISCUSSION

In this study, patients with CP who showed early pain reduction during 6-month indwell of an FCSEMS and subsequently maintained good pain relief until 6 months after FCSEMS removal represented only one-third of those eligible for the primary efficacy analysis. This is clearly inferior to the expected outcomes. In addition, procedure-related SAEs were observed in almost one-third of patients and study stent migrations occurred in nearly half of patients (though most were asymptomatic).

Because pain is the most frequent cause for hospitalization and the strongest predictor of poor QOL in patients with CP,¹ effective pain management is a key treatment goal. Although surgery is considered the most definitive treatment, endotherapy is usually undertaken initially given the invasiveness of surgery and the relatively low morbidity and mortality of endoscopy.²⁹ The best responders to endoscopic therapy are patients with obstructing stones located in the head of the

pancreas, complete stone clearance and absence of main PD stricture, with a short disease duration and a low frequency of pain attacks before endoscopic therapy, together with the discontinuation of alcohol and tobacco.³⁰ In patients with uncomplicated painful CP and a dilated main PD, endoscopic therapy is recommended as first-line treatment after failed medical therapy following discussions by a multidisciplinary team.³⁰ In obstructive CP, endotherapy is the preferred initial treatment and provides early and sustained pain relief in 88% and 67% of patients, respectively.³¹

Optimal timing of surgery is uncertain, but 2018 evidence-based guidelines from a United European Gastroenterology working group concluded that surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP, and that early surgery is favored over surgery at a more advanced stage of the disease.³⁰ Consistent with this recommendation, a 2020 RCT reported that complete or partial pain relief at end of follow-up was achieved in 58% (23/40) patients in an early surgery group vs. 39% (16/41) patients in the endoscopy-first approach group ($P = .10$).³² However, at the end of follow-up, pain scores and proportion of patients with complete or partial pain relief, pancreatic function and QOL were not significantly different between groups in this RCT.³² A 2021 meta-analysis⁵ concluded that endoscopic interventions can be considered first in cases with the possibility of reaching PD clearance or relief of obstruction, since decompression surgery would not achieve additional benefit for this symptom if it does not improve after endoscopic therapy. Surgery could then be performed when there is a recurrence of a stricture or pancreatolithiasis, or in the event of a failure with endoscopic treatment. The authors acknowledged that this approach is recommended in several published clinical practice guidelines.^{7,33,34}

Using SEMS for stricture calibration might shorten the calibration period and avoid repeated procedures for stent exchange. However, our results did not suggest a benefit for FCSEMS therapy in all patients with CP-associated pain. The two groups that appeared to benefit showed an early response after FCSEMS placement or plastic stent placement with subsequent exchange for a FCSEMS, with pain relief that was durable throughout the 6-month post-stent removal follow-up period. These preliminary findings might warrant future studies in patients with painful CP who have a favorable pain response to initial ductal decompression with a single plastic stent, and randomly comparing 180-day treatment with multiple plastic stents vs a single FCSEMS, or randomly comparing early surgery to 180-day FCSEMS treatment with multi-year follow-up in a similar patient population.

Our study had several limitations. This was a single-arm study conducted by expert endoscopists at large university medical centers. The results might not be replicable at centers with lower procedural volumes, less experience with pancreatic endotherapy, or with fewer specialty resources. Pain relief reported by end of study could be attributable to an increase in narcotic dose when that occurred. The 6-month follow-up period after FCSEMS removal may have been short for adequate estimation of PD stricture recurrences. Several authors disclosed financial relationships with the manufacturer of the study FCSEMS.

Conclusions

In patients with painful CP, a PD stricture and upstream PD dilation who received 6-month treatment with a new FCSEMS, the performance goal for the primary endpoint of pain relief was

not reached, and SAEs were common. Further study is needed to clarify optimal FCSEMS design and appropriate patient populations for this treatment.

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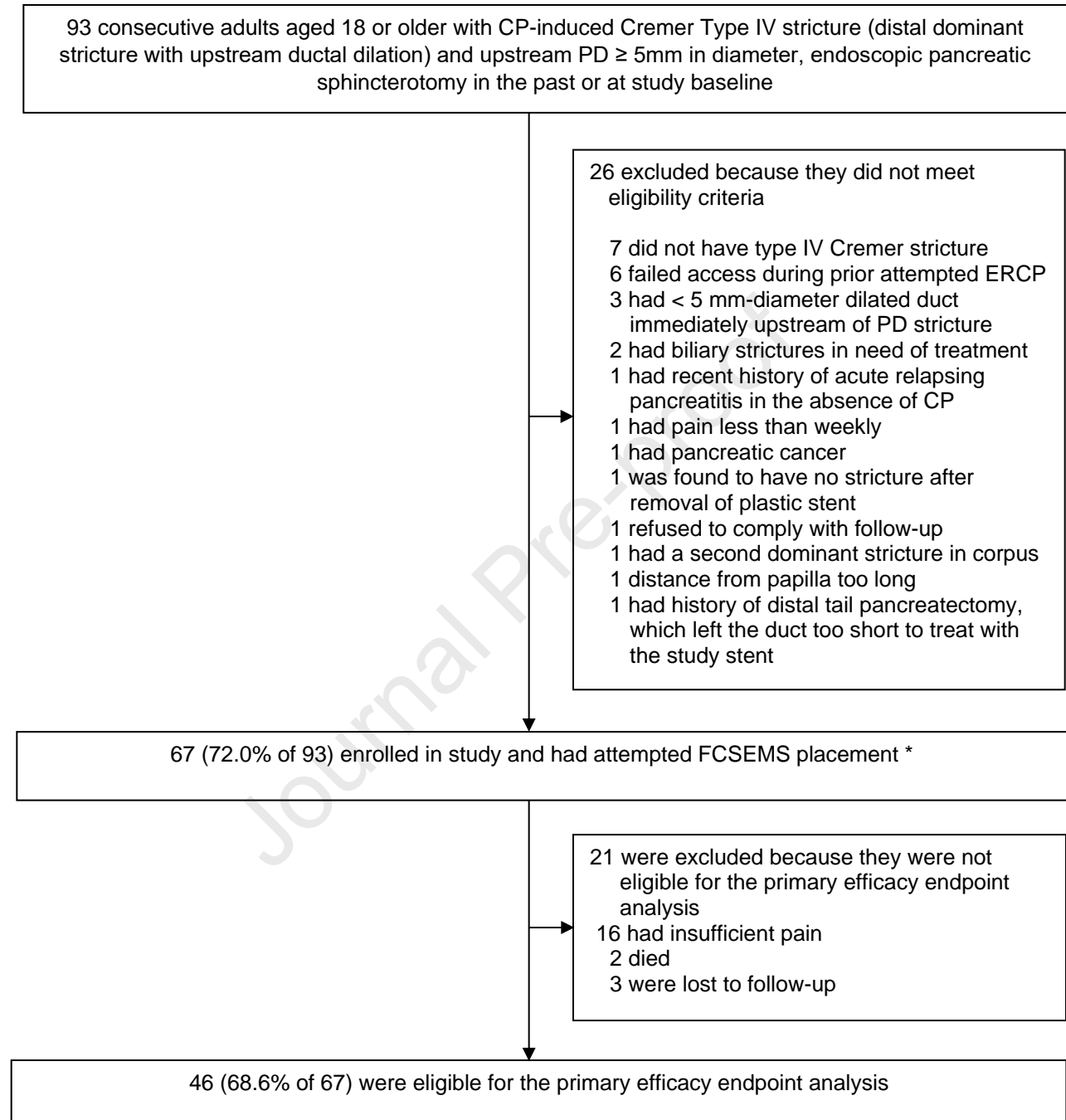
DATA SHARING

The data, analytic methods, and study materials for this study may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy

(<http://www.bostonscientific.com/en-US/data-sharing-requests.html>).

Figure 1. Pancreatic “soft” fully-covered self-expanding metal stent tested in this study. The membrane extends proximally over the metal meshes with the aim of reducing friction with the pancreatic duct epithelium



Figure 2. Patient flow through the study

CP chronic pancreatitis PD pancreatic duct
 ERCP endoscopic retrograde cholangiopancreatography
 FCSEMS fully-covered self-expanding metal stent

* Sixty-five (97.0%) of these had successful FCSEMS placement and subsequent FCSEMS removal or observation of complete distal migration at 6 months.

Table 1. Patient demographics and baseline characteristics on ITT analysis set (N=Error! Reference source not found.)

	Mean \pm SD (n) (range) or % (n/N)
Age (years)	52.7 \pm 12.5 (67) (20.0, 76.0)
Male	62.7% (42/67)
Time since CP diagnosed (years)	6.4 \pm 6.4 (23) (0.1, 27.7)
Race	
Not Hispanic or Latino	100.0% (67/67)
Ethnicity	
Asian	10.4% (7/67)
Black or African American	9.0% (6/67)
White (Caucasian)	80.6% (54/67)
Weight (kg)	71.5 \pm 18.4 (67) (45.0,115.6)
CP etiology	
Gallstones	1.5% (1/67)
Alcoholic	49.3% (33/67)
Current alcohol consumption	11.9% (8/67)
Smoking	35.8% (24/67)
Hereditary	4.5% (3/67)
Other	11.9% (8/67)
Unknown	28.4% (19/67)
CP calcific	71.6% (48/67)
Unknown	1.5% (1/67)
Type of calcification	
Ductal	41.7% (20/48)
Parenchymal	18.8% (9/48)
Both	39.6% (19/48)
Surgical candidate	68.7% (46/67)
Unknown	13.4% (9/67)
Smoking status	
Current	53.7% (36/67)
Previous	25.4% (17/67)
Never	20.9% (14/67)
Narcotic dose (MME)	31.9 \pm 52.3 (65) (0.0,240.0)
Time since first narcotic medication (years)	4.8 \pm 7.3(28) (0.0,35.6)
Steatorrhea	19.4% (13/67)
Diabetes Status	
Diabetic	37.3% (25/67)
Insulin Dependent	29.9% (20/67)
Oral Medication	7.5% (5/67)
Pancreas divisum	26.9% (18/67)
Prior pancreatic sphincterotomy performed	70.1% (47/67)
Prior biliary or pancreatic sphincterotomy performed	71.6% (48/67)
History of pancreatic duct stones	55.2% (37/67)
Unknown	6.0% (4/67)
Stone clearance procedures performed	79.5% (31/39)
ESWL	51.6% (16/31)
Balloon	64.5% (20/31)
Basket	16.1% (5/31)
Other	3.2% (1/31)
Current pancreatic stones	62.7% (42/67)
Largest stone (mm)	6.2 \pm 3.9 (40) (1.0,20.0)

Table 2. Study stent procedure characteristics on ITT analysis set (N=67)

	Median (n) (range) or % (n/N)
Inpatient procedure	44.8% (30/67)
Inpatient stay (days)	2.0 (30) (1.0,7.0)
Procedure time (mins)	25.0 (67) (7.0,117.0)
Placement of stent in papilla	
Major	71.2% (47/66)
Minor	28.8% (19/66)
Pancreatogram performed prior to stent	98.5% (65/66)
Prophylatic antibiotics administered	64.2% (43/67)
Prophylatic NSAIDs administered	53.7% (36/67)
Biliary sphincterotomy performed prior to or during study	59.7% (40/67)
Pancreatic sphincterotomy performed prior to or during study	100.0% (67/67)
Previously placed pancreatic stent removed	56.7% (38/67)
Biliary stent placed (plastic)	1.5% (1/67)
Pancreatogram performed after stent placement	51.5% (34/66)
Anatomy of pancreatic duct	
Normal	61.2% (41/67)
Patent Santorini	6.0% (4/67)
Pancreas Divisum	25.4% (17/67)
Other	6.0% (4/67)
Other endoscopic procedures performed	70.1% (47/67)
Pancreatic stone extraction (other than ESWL)	40.3% (27/67)
Balloon sweep	46.3% (31/67)
Other	23.9% (16/67)

Figure 3. High grade stricture of the dorsal pancreatic duct in a chronic pancreatitis patient with divisum (A). Figures B and C demonstrate stent placement. Figure D shows expanded stent in good position. The arrow demonstrates the stricture site which will be progressively dilated with the SEMS.

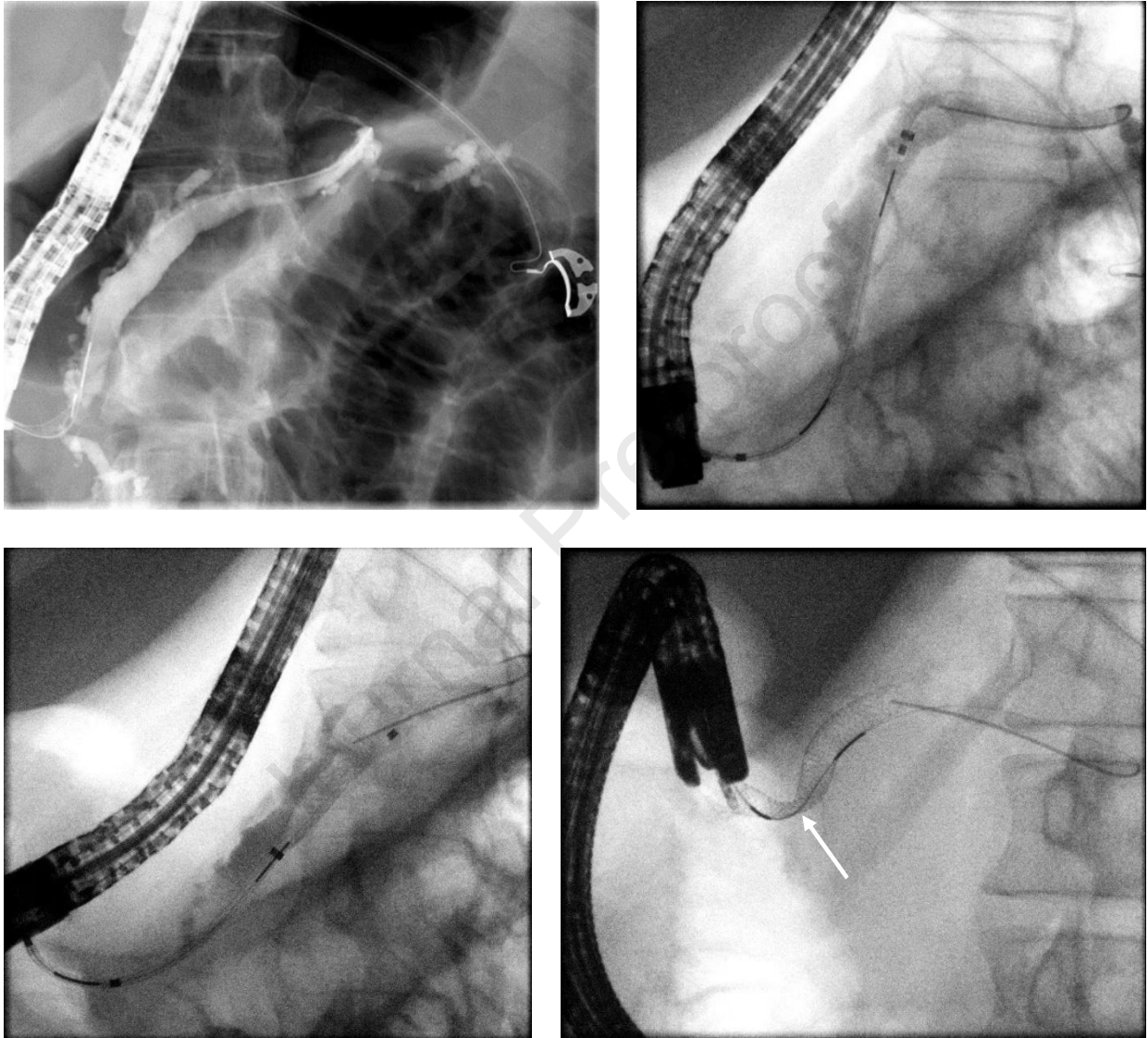


Table 1. Primary efficacy and safety endpoint analysis

	Rate	PG	Lower 95% CI	P value ³
Primary efficacy endpoint¹				
ITT	26.1% (12/46)	53.0%	14.3%	0.999
	Rate	PG	Upper 95% CI	P value ³
Primary safety endpoint²				
ITT	31.3% (21/67)	32.0%	43.8%	0.513

ITT intention to treat PG performance goal

1 – Based on mean of VAS Pain Score and Izbicki Frequency of Pain subscore, with score ranging from 0 to 100. For patients with a prior plastic pancreatic stent, baseline was considered to be the time of study stent placement. For patients without a plastic pancreatic stent, baseline was the time of enrollment. Defined as either complete (pain score \leq 10) or partial (pain reduced by 50%) pain relief reported at 6 months post-removal without an increase in narcotics dose by 50%.

2 – Rate of related SAEs with pain thought to be caused by WallFlex Pancreatic stent expansion were reported, but did not count towards the endpoint if all three of the following conditions applied:

Pain could be managed by medication, with the exception of injectable narcotic use for more than 24 hours.

Pain did not cause WallFlex Pancreatic stent removal.

Pain resolved by 72 hours after WallFlex Pancreatic stent placement.

3 – P-value<0.025 meant the performance goal was met.

Table 4. Main related Serious Adverse Events related to FCSEMS or study procedures on ITT analysis set (N=Error! Reference source not found.)

Serious adverse event*	Number of events	% (n/N patients)
Any serious adverse event	29	31.3% (21/67)
Pain	12	14.9% (10/67)
Post-ERCP pancreatitis	8	11.9% (8/67)
Chronic pancreatitis exacerbation	3	4.5% (3/67)
Duodenal ulceration	1	1.5% (1/67)
Elevated liver function tests	1	1.5% (1/67)
Ampullary occlusion of the bile duct [†]	1	1.5% (1/67)
Peripancreatic fluid collection [†]	1	1.5% (1/67)
Portal vein and SMV thrombosis [†]	1	1.5% (1/67)
Fatal multiorgan failure from sepsis [†]	1	1.5% (1/67)

FCSEMS fully-covered self-expanding metal stent ITT intention to treat

ERCP endoscopic retrograde cholangiopancreatography SMV superior mesenteric vein

*Rows are not mutually exclusive.

[†]These SAEs occurred in one patient.

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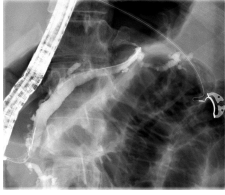
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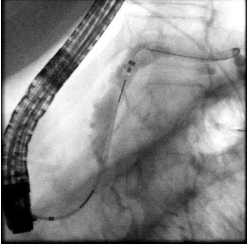
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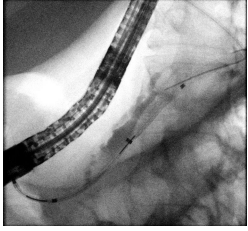
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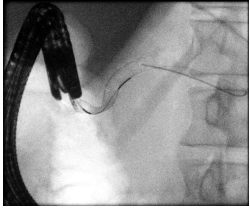
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**Sherman et al. Soft Self-expanding Metal Stent to Treat Painful Pancreatic Duct Strictures
Secondary to Chronic Pancreatitis: A Prospective Multicenter Trial**

Acronyms and abbreviations

CDM: complete distal migration

CI: confidence interval

CP: chronic pancreatitis

ERCP: endoscopic retrograde cholangiopancreatography

ESWL: extracorporeal shock wave lithotripsy

EUS: endoscopic ultrasound

FCSEMS: fully covered self-expanding metal stent

FDA: US Food and Drug Administration

IDE: Investigational Device Exemption

ITT: intention to treat

MME: morphine milligram equivalents

PD: pancreatic duct

PG: performance goal

QOL: quality of life

RCT: randomized clinical trial

SAE: serious adverse event

SAS: Statistical Analysis System

SD: standard deviation

VAS: Visual Analogue Scale