Clinical Investigation Plan

A Prospective, Multi-Center, Single Arm, Non-Inferiority, Open-Label, Pivotal Study to Evaluate the Effectiveness and Safety of Endoscopic Ultrasound-Guided Transluminal Drainage with 'Niti-S SPAXUS™ Stent' for the Treatment of Pancreatic Pseudocyst

CIP No. : SPAXUS-001

Version No. : 1.3

Version Date : August 05, 2016

TAEWOONG MEDICAL CONFIDENTIAL

Clinical Investigation Plan Agreement

I have read and reviewed this clinical investigation plan thoroughly, and understood and got the knowledge of its contents sufficiently. I, therefore agree to proceed with the clinical study by signing on this agreement. I assure you that I will proceed this clinical study in accordance with the Helsinki Declaration and the ethical principles of the Institutional Review Board (IRB), all relevant regulations, including the clinical investigation plan, standard operating procedures, the International Conference on Harmonization and Good Clinical Practice (ICH-GCP) guidance and ISO 14155.

Taewoong Medical Co., Ltd.		
Sponsor		
Kyung-Min Shin		
Name of CEO	Signature	Date

Investigational Institution		
Name of Principal Investigator	Signature	Date

<Synopsis of Clinical Study Protocol>

Title	A prospective, multi-center, single arm, non-inferiority, open-label, pivotal study to evaluate the effectiveness and safety of endoscopic ultrasound-guided transluminal drainage with 'Niti-S SPAXUS™ Stent' for the treatment of pancreatic pseudocyst
Study Objective	The objective of this study is to evaluate the effectiveness and safety of Niti-S SPAXUSTM Stent, a lumen-apposing, fully covered, self-expandable metal stent, being used for EUS (endoscopic ultrasound)-guided transluminal drainage for the treatment of pancreatic pseudocyst through this clinical study.
Investigational Institution / Principal Investigator	1. Jong Ho Moon, Department of Gastroenterology, Soon Chun Hyang University Bucheon Hospital 2. Sang Soo Lee, Department of Gastroenterology, Asan Medical Center 3. Jong Kyun Lee, Department of Gastroenterology, Samsung Medical Center 4. Seung-Ok Lee, Department of Gastroenterology, Chonbuk National University Hospital 5. Chang Min Cho, Department of Gastroenterology, Chilgok Kyungpook National University Medical Center 6. Se Woo Park, Department of Gastroenterology & Hepatology, Hallym University Dongtan Sacred Heart Hospital
Indication / Study Population	The Niti-S SPAXUS™ Stent is intended for the drainage of a pancreatic pseudocyst. Patients diagnosed with pancreatic pseudocyst which is more than 6 cm in size having more than 70% of fluid content
Number of Subjects	35 patients (including drop-out rate 10%)
Investigational Medical Device	Niti-S SPAXUS™ Stent [Orthopaedics, B03000] *As a newly developed medical device, there is no designated subcategory.*
Study Design	The study is designed to be conducted as a prospective, multi-center, single arm, non-inferiority, open-label study to evaluate the safety and effectiveness of Niti-S SPAXUS™ Stent, being used for EUS-guided transluminal drainage in a total of 35 patients with pancreatic pseudocyst at 6 centers.
Study Methods	1. Among the patients who are diagnosed with pancreatic pseudocysts through abdominal ultrasound, endoscopic ultrasound, CT or MRI, those patients who require EUS-guided transluminal drainage will be referred to this study.

Study Methods	2. After hearing enough information from the investigator and signing the informed consent form voluntarily, the patient will be enrolled in this clinical study if he or she meets all the criteria for subject inclusion and exclusion. 3. Pre-procedural treatment will be conducted to the subjects enrolled in this study in accordance with the critical standard of each institution and they will undergo the procedures with the Niti-S SPAXUS™ Stent on the scheduled day. 4. After the Niti-S SPAXUS™ Stent procedure, the subject will visit the hospital in accordance with the schedule specified in the clinical investigation plan and receive the follow-up observation. At Day 30~60 after the procedure, blood tests, clinical symptoms, and abdominal CT scans will be performed to evaluate the clinical success, and then the stent will be removed. Within 20 days after removal of the stent, assessment of safety and effectiveness will be performed through blood tests, clinical symptoms and radiological examination (X-ray). 5. The clinical study will be closed out if all follow-up examinations are completed and no adverse events have occurred or any adverse events have already been resolved at Day 20 after removal of the stent.
Study Period	It is expected that it will take about 15 months from the approval of the Ministry of Food and Drug Safety and the IRB, including the subject enrollment period of about 12 months and the follow-up period of 3 months at maximum.
Inclusion criteria	• Male and female adults over 19 years of age • Patients diagnosed with pancreatic pseudocyst who satisfy the following criteria and who require the drainage treatment - When the size of the pseudocyst is 6 cm and larger (based on the maximum cross-sectional area on CT) - When the fluid content of the pseudocyst is more than 70% - When the pseudocyst is in a position to allow transluminal drainage • When the patient is willing to participate in the clinical study, to comply with treatments and procedures, and to visit the hospital for all follow-up evaluations • When the patient heard a description of the purpose, method and effectiveness of this clinical study and has voluntarily signed a written informed consent

Exclusion criteria	• When the patient cannot use appropriate contraception as a woman of childbearing age, or when the patient is pregnant or breastfeeding • When the patient is not possible to undergo the endoscopic intervention • When an effective drainage is difficult due to severe septation in pseudocysts • When the patient is severely allergic to contrast agent and Nitinol, etc. • When the patient has a hemorrhagic disease or coagulation disorder (e.g. DIC) • When the platelet count is less than 60,000 cells/mm^3 or exceeds the International Normalized Ratio (INR) 1.5 • When the patient has hemodynamic instability (e.g. shock) • When the patient has immunosuppressive diseases such as malignant tumors and bone marrow transplantation, or is receiving immunosuppressive treatments such as chemotherapy or immunosuppressive drugs • If the patient has any active infectious disease requiring antibiotic treatment, such as known or suspected meningitis or endocarditis • If the patient has any psychiatric illness or conditions that makes participation in the clinical study impossible (e.g. dementia, seizure) • If the patient has participated in other clinical studies for medicines or medical devices within the last 3 months. • When the investigator determines that the Niti-S SPAXUS™ Stent procedure is not possible for the patient
Effectiveness Endpoints	1) Primary Effectiveness Endpoints • Clinical success 2) Secondary Effectiveness Endpoints • Technical Success • Stent Lumen Patency • Stent Removal Success • Procedure Time
Safety Endpoints	• Procedural / Device related serious adverse events • Other adverse events
Potential Adverse Events	<Expected adverse events during the stent procedure> • Bleeding • Stent misplacement • Inadequate expansion • Stent migration • Pain

	• Perforation < Expected adverse events post stent placement> • Bleeding • Pain • Perforation • Stent misplacement • Stent migration • Stent occlusion • Fever • Pancreatitis • Abscess formation • Vomiting • Pneumoperitoneum • Intraperitoneal leakage • Peritonitis • Hematoma • Inflammation • Infection • Fistula • Ulceration • Sepsis • Rupture of intra-cystic artery • Stent removal failure
Analysis Sets	The analysis of clinical success and the effectiveness endpoints will be conducted in FAS (Full Analysis Set) as the main analysis population, while the analysis of the safety endpoints will be conducted in the Safety Set. • SS (Safety Set) All subjects who attempted to receive the Niti-S SPAXUS™ Stent procedure among those who satisfied the inclusion/exclusion criteria and gave the informed consent for participation in this clinical study. • FAS (Full Analysis Set) Subjects who underwent the Niti-S SPAXUS™ Stent procedure and completed the primary effectiveness assessment among those who satisfied the inclusion/exclusion criteria and gave the informed consent for participation in this clinical study. • PP (Per Protocol) Set Subjects who have completed the study with no serious violation of the clinical investigation plan among those who satisfied the FAS.

Statistical Method	1) Primary Effectiveness Assessment To assess the primary effectiveness at the time of stent removal (Day 30 or 60 after the procedure), the number and proportion of subjects who achieved clinical success of stenting procedure were presented and the reference value (96%) and 97.5% single-tailed confidence interval is to be obtained for the confirmation of the degree of non-inferiority for the difference from the reference value. If the lower limit of confidence interval is greater than -10%, it will be considered that the non-inferiority is confirmed. 2) Secondary Effectiveness Assessment For such as technical success, stent lumen patency, and stent removal success, which are the secondary effectiveness endpoints, the frequencies and percentages by each visit will be presented while for the procedure time, the mean and 95% confidence interval will be presented. 3) Safety Evaluation For the procedure or the medical device-related serious adverse events which are the safety evaluation variables, the frequency and percentage as well as 95% confidence interval will be presented. For all other adverse events, the frequency and percentage of subjects will be presented in a listing.

< Clinical Study Schedule >

Study Procedure	Screening	Date of Procedure	Treatment Period		End of Treatment [§] (Removal of Stent)		End of Study
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 5-1	Visit 6
	Baseline	Day 1	Day 2	Day 5 ±2 days	Day 30 ±10 days	Day 60 ±10 days	Post stent removal 20 day± 10 days
	Out-patient/In-patient	In-patient	In-patient	In-patient	In-patient	In-patient	Out-patient
Informed Consent	√						
Inclusion/Exclusion Criteria	√						
Demographics	√						
Physical Measurement	√						
Vital Signs [1)]	√	√	√	√	√	√	√
Physical Examination	√		√	√	√	√	√
Medical History / Allergy [2)]	√						
Laboratory tests							
• Hematological test [3)]	√	√	√	√	√	√	√
• Blood Coagulation Test [4)]	√	√	√	√	√	√	√
• Serum chemistry test [5)]	√	√	√	√	√	√	√
• Pregnancy Test [6)]	√						
Clinical Symptoms [7)]	√	√	√	√	√	√	√
Abdominal CT [8)]	√				√	√	
Radiological Examination (X-ray) [9)]	√	√	√	√			√
SPAXUS stent procedure [10)]		√					
SPAXUS stent removal [11)]					√	√	
Clinical success evaluation [12)]					√	√	
Technical success evaluation [13)]		√					
Concomitant medications /procedures	√	√	√	√	√	√	√
Adverse event /Serious Adverse event		√	√	√	√	√	√

1) Vital signs include blood pressure, pulse rate, respiratory rate, and body temperature.

2) Medical history and allergy information includes important past medical and surgical history, medication and other allergies.

3) The items of the hematologic test are as follows. The baseline test should be performed within 7 days of the procedure, and after the stenting procedure at visit 2 (day of the procedure).
WBC, RBC, Hematocrit, Hemoglobin, Platelet, WBC differential count (Eosinophils, Basophils, Band Neutrophils, Segmented Neutrophils, Lymphocytes, Monocytes)

4) The blood coagulation test includes PT, aPTT and INR. The baseline test should be performed within 7 days of the procedure, and after the stenting procedure at visit 2 (day of the procedure).

5) The serum chemistry test items are as follows. The baseline test should be performed within 7 days of the procedure, and after the stenting procedure at visit 2 (day of the procedure).
Total bilirubin, Direct bilirubin, AST, ALT, Alkaline Phosphatase, γ-GT, glucose, Amylase, Lipase, CRP

6) The pregnancy test should be performed within 48 hours of the procedure in women of childbearing ages, using a urine test (or β-HCG) for confirmation.

7) Clinical symptoms include abdominal pain, nausea, vomiting, and et al. and will be assessed through inquiries by the investigator.

8) The abdominal CT scan for screening should be performed within 6 months of the procedure and the tests conducted at external hospitals are also usable. The abdominal CT scan must be performed to evaluate the clinical success and to ensure the stent removal at Day 30~60 after the procedure.

9) The Radiological examination (X-ray) includes the images of abdomen, and the X-ray for screening should be performed within a month of the procedure. Additional photos may be taken if necessary at the discretion of the investigator.

10) EUS-guided transluminal drainage will be performed using a SPAXUS stent.

11) At Day 30 after the procedure, the stent will be removed using endoscopic forceps or snare according to the standard procedure, if the stent removal criteria are met, at the discretion of the investigator, based on the laboratory test results, clinical symptoms, and abdominal CT scan. However, if the removal criteria are not satisfied at Day 30 after the procedure at the discretion of the investigator, it will be assessed whether the stent can be removed or not at Day 60 after the procedure and the Niti-S SPAXUS^{TM} stent will be removed at the maximum Day 60 after the procedure. If the pancreatic pseudocyst is not resolved at Day 60 after the procedure, the Niti-S SPAXUS^{TM} stent will be removed and a plastic stent will be inserted.

12) The clinical success will be assessed by the investigator based on the size of the pancreatic pseudocyst confirmed from the abdominal CT scanning.

13) The technical success will be assessed by the investigator based on the position, deployment and fluid status drained of the SPAXUS stent.

§ For the end of treatment (EOT) visit, the visit 5 will be conducted at Day 30 after the procedure and the removal of the stent will be confirmed. If the removal criteria are not met at the discretion of the investigator, visit 5-1 will be conducted at Day 60 after the procedure. At the visit, the investigator will assess the clinical success of the pancreatic pseudocyst and will remove the Niti-S SPAXUS^{TM} Stent.

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ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	active Partial Thromboplatin Time
AST	Aspartate Aminotransferase
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRP	C-Reactive Protein
CT	Computed Tomography
DIC	Disseminated Intravascular Coagulopathy
EOT	End of Treat
EUS	Endoscopic Ultrasound
FAS	Full Analysis Set
FDA	Food Drug Administrative
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator’s Site File
ISO 14155	International Organization for Standardization 14155
LACSEMS	Lumen-Apposing Covered Self-Expanding Metal Stent
MRI	Magnetic Resonance Imaging
PFC	Pancreatic Fluid Collection
PP	Per Protocol
PPs	Pancreatic Pseudocyst
PT	Prothrombin Time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SOP	Standard Operating Procedures

SS	Safety Set
UADE	Unexpected Adverse Device Effect
WBC	White Blood Cell
WON	Walled-Off Necrosis
β-HCG	Beta Human Chorionic Gonadotropin
γ-GT	Gamma Glutamyl Transferase

1. STUDY TITLE

A prospective, multi-center, single arm, non-inferiority, open-label, pivotal study to evaluate the effectiveness and safety of endoscopic ultrasound-guided transluminal drainage with 'Niti-S SPAXUS ™ Stent' for the treatment of pancreatic pseudocyst

2. NAMES AND LOCATIONS OF INVESTIGATIONAL INSTITUTIONS

- Soon Chun Hyang University Bucheon Hospital
  170 Jomaru-ro, Wonmi-gu, Bucheon-si, Gyeonggi-do (14584)
- Asan Medical Center
  88, Olympic 43-gil, Songpa-gu, Seoul (05505)
- Samsung Medical Center
  81, Ilwon-ro, Gangnam-gu, Seoul (06351)
- Chonbuk National University Hospital
  20, Geonji-ro, Deokjin-gu, Jeonju-si, Jeollabuk-do (54907)
- Chilgok Kyungpook National University Medical Center
  807, Hoguk-ro, Buk-gu, Taegu-si, Gyeongsangbuk-do (41404)
- Hallym University Dongtan Sacred Heart Hospital
  7, Keunjaebong-gil, Hwasung-si, Gyeonggi-do (18450)

3. NAMES AND POSITIONS OF PRINCIPAL INVESTIGATORS, SUB INVESTIGATOR AND CO-INVESTIGATOR OF THE STUDY

- Coordinating Investigator

  Jong Ho Moon, Department of Gastroenterology, Soon Chun Hyang University Bucheon Hospital

- Principal Investigators

Investigational Institution	Affiliation	Name	Contact
Soon Chun Hyang University Bucheon Hospital	Department of Gastroenterology	Jong Ho Moon	032-621-5094
Asan Medical Center	Department of Gastroenterology	Sang Soo Lee	02-3010-3187
Samsung Medical Center	Department of Gastroenterology	Jong Kyun Lee	02-3410-3409
Chonbuk National University Hospital	Department of Gastroenterology	Seung-Ok Lee	063-250-1289
Chilgok Kyungpook National University Medical Center	Department of Gastroenterology	Chang Min Cho	053-200-2608
Hallym University Dongtan Sacred Heart Hospital	Department of Gastroenterology & Hepatology	Se Woo Park	031-8086-2858

- Co-Investigator and Sub Investigators

  See Appendix 1.

4. NAMES AND POSITIONS OF INVESTIGATIONAL MEDICAL DEVICE MANAGER AND MONITORING STAFF

- Investigational Medical Device Manager
  See Appendix 1.

- Clinical Research Associate (CRA)
  See Appendix 2.

5. NAME AND ADDRESS OF SPONSOR

Name of the Company	CEO	Address	Contact
TaeWoong Medical Co., Ltd.	Kyung-Min Shin	14, Gojeong-ro, Wolgot-myeon, Gimpo-si, Gyeonggi-do	031-904-6153

6. INTRODUCTION

6.1. Background

A pancreatic pseudocyst usually occurs on the external side of the pancreas after 4 weeks from the onset of interstitial pancreatitis, which is a fluid collection created by a continuous leakage of pancreatic juice from the pancreatic duct without necrosis of parenchymal necrosis in a sac composed of inflammatory wall [1)]. The incidence of pseudocyst in acute pancreatitis is about 5 to 16% and about 20 to 40% in chronic pancreatitis [2-5)]. Although some studies reported that 86% of pancreatic pseudocysts disappear spontaneously, but if they do not disappear naturally, it can lead to serious complications such as rupture or hemorrhage [6)].

Methods to treat a symptomatic pancreatic pseudocyst include surgical treatments such as cyst-enteric anastomosis, which connects the gastrointestinal tract with the cysts, and non-surgical treatments such as percutaneous or endoscopic drainage. The surgical treatments such as a cyst-enteric anastomosis has a risk of complications due to general anesthesia and laparotomy known to have the morbidity of 7 to 10%, and the mortality of 0 to 6% [7-9)]. The percutaneous drainage among the non-surgical treatments has a risk of infections through subcutaneous layer and protracted presence of an indwelling catheter for several weeks can cause the formation of pancreatocutaneous fistula [10)]. The endoscope-guided drainage is a method to create a connected pathway between the pancreatic pseudocyst and the gastric lumen to drain the fluid. It is less invasive than open surgery and can avoid the risk of complications from general anesthesia as well as recover quickly. It has emerged as a therapeutic alternative to surgery.

Endoscope-guided drainage may be performed by a transpapillary or a transmural approach, dependent upon the presence of connection between the pancreatic duct to the pseudocyst. The transpapillary drainage has a lower risk of bleeding and perforation compared to the transmural approach but it has a risk of pancreatic duct damage by the drainage tube and a disadvantage of low pseudocyst resolution rate. The transmural drainage is a technique in which a plastic stent or a metal stent is inserted into a pancreatic pseudocyst and drains the collected fluid into the stomach or duodenum by puncturing. The previous studies reported that the clinical success rate was 70 to 87% and the incidence rate of complications was 11 to 34% [12-14)]. However, the endoscopy guided drainage is difficult to puncture accurately into the pancreatic pseudocyst as a blind approach, and has a risk of hemorrhage because the anatomical location between the pseudocyst and the gastrointestinal tract, and the vascular distribution cannot be confirmed. Because of such risks, the endoscopic ultrasound-guided drainage is widely used because it has a Doppler function and allows accurate identification of the anatomical location between the pseudocyst and the gastroenteric tract as well as the vascular distribution.

The plastic stent in the sizes ranged 7 to 10Fr which can be used for EUS-guided transmural drainage can prevent the stent migration, but is disadvantageous as its inner diameter is narrow which can cause the stent occlusion and requires frequent exchange of the stent or additional stent insertion and incomplete draining. For this reason, a fully covered, self-expandable biliary metal stent with a larger internal diameter was used for EUS-guided transmural drainage. In addition, it was possible to drain

the pancreatic pseudocyst within a short period of time while maintaining the stent lumen patency for a longer period of time by inserting a metal stent, however, problems including the leakage and infection of the encapsulated contents in the pancreatic pseudocyst due to stent migration and mucosal injury have occurred [15,16]. In order to overcome these metal stent migration-induced problems, a lumen-apposing, fully-covered, self-expandable metal stent that is barbell-shapeed has been developed. It was approved and is being used in the US and Europe, and has been reported with good clinical success rates of 86 to 100% [17-19]. However, there are currently no approved products available in Korea.

The 'Niti-S SPAXUS^{TM} Stent' developed is a silicone-coated, self-expandable stent consisted of a nitinol wire woven in a cylindrical mesh which is used for the EUS-guided transluminal drainage. There are three types of lumen diameters: 8, 10, and 16 mm. The total length is 20 mm, and the distance between the bilateral end flanges after deployment is 5 mm. The flanges of both ends are structured to fold back after deployment to prevent stent migration or leakage, and the edges are designed to minimize mucosal or tissue damage. 'Niti-S SPAXUS^{TM} Stent' has the flanges of both ends flexible compared to existing products, and its introducer system is 10Fr in outer diameter, which is smaller than conventional products. Its operation is simple and its usage is same with that of existing metal stents having an advantage of being familiar for the user.

In a preclinical study, the Niti-S SPAXUS^{TM} Stent was technically feasible and successfully inserted and removed in the target area without complication. Endoscopic intervention via stent was possible and no stent migration was observed. It was also reported that all lesions of patients applied with 'Niti-S SPAXUS^{TM} Stent' have been resolved [20].

This study was planned based on the background described above to confirm the effectiveness and safety of 'Niti-S SPAXUS^{TM} Stent' made of Nitinol as a lumen-apposing, fully-covered and self-expanding metal stent developed in Korea used for EUS-guided transluminal drainage,.

6.2. Clinical Experience of EUS-guided Transluminal Drainage

1) Pre-clinical Study of Niti-S SPAXUS^{TM} Stent

Moon JH, Choi HJ, Kim DC, et al. A newly designed fully covered metal stent for lumen apposition in EUS-guided drainage and access: a feasibility study (with videos). Gastrointest Endosc. 2014 Jun;79(6):990-5.

This study reports the results of animal experiments and clinical application of a new design lumen apposing stent. The Niti-S SPAXUS^{TM} Stent is a silicone-coated, self-expandable metal stent consisted of nitinol wires. The diameter of the flange at both ends was 25 mm to anchoring. After deployment, the anchoring flanges can be folded back to hold the 2 luminal interfaces in apposition. The stent diameters are 8, 10, and 16 mm, and the length is 20 mm, but the distance between the flanges is 5 mm after folding back with deployment.

Six small pigs weighing 25 to 35 kg were used for the animal study. One week before the study, the orifice of the ampulla of Vater for the bile duct was ligated with endoscopic clipping to provoke an

enlarged GB. A cholecystogastrostomy tract was created under EUS guidance, and the stent was deployed across the lumen under EUS, fluoroscopic, and endoscopic guidance. Contrast was injected in the GB through the stent to confirm the absence of leakage. Cholecystoscopy was performed immediately. The stent was removed at 4 weeks, and cholecystoscopy was performed again after the stent removal.

Total 7 patients underwent EUS-guided stent placement for lumen apposition for acute cholecystitis (AC) of the bile duct or GB cancer in 3 patients and symptomatic pancreatic fluid collection (PFC) in 4 patients. In patients with PFC, after confirmation that the PFC had completely resolved on CT, the stent was removed endoscopically after complete disappearance of the PFC confirmed by CT scan.

the stent was successfully inserted and deployed in the GB via a transgastric approach under EUS guidance without adverse events in all 6 pigs. Contrast injection demonstrated the absence of leakage. Cholecystoscopy with enhanced endoscopy was performed successfully in all animals after stent placement. All stents were intact and were removed successfully at 4 weeks. The stents were successfully deployed without adverse effects in 7 patients. AC or PFC was resolved after stent placement in all patients. Endoscopic procedures were possible through the stent. Stent migration was not observed. The stent was successfully removed from the 4 patients with PFC after complete resolution.

In conclusion, Transenteric drainage and endoscopic intervention by using a novel fully covered self-expandable metal stent for lumen apposition under EUS guidance is feasible for the management of AC and PFC.

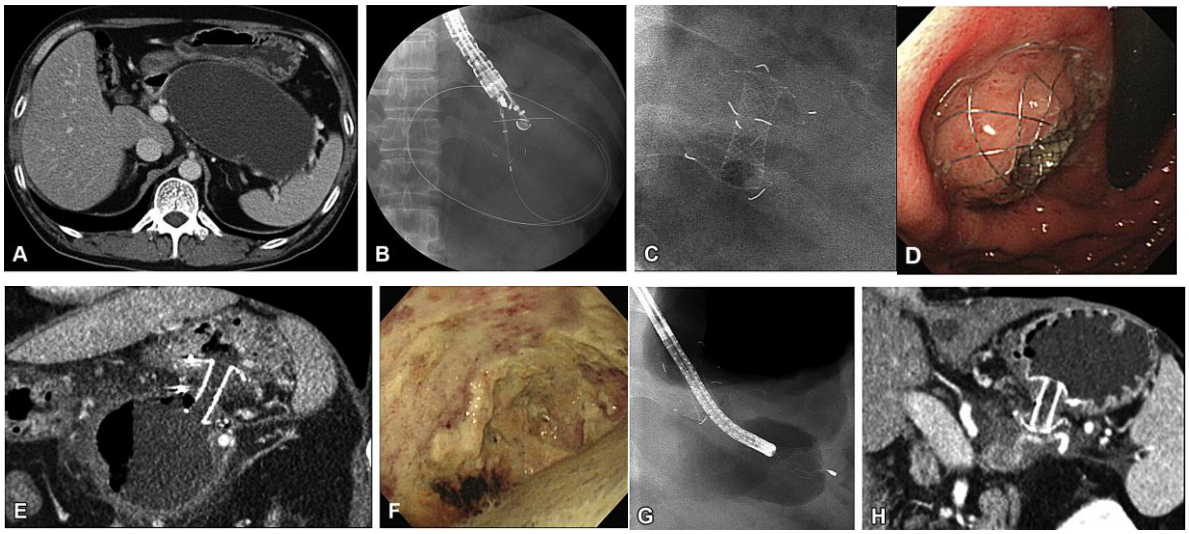


Figure 4. Transgastric EUS-guided pancreatic pseudocyst (PPC) drainage by using the new stent for lumen apposition. A, CT showing PPC. B, Deploying the stent on a PPC. C-E, Fully deployed stent (C, radiograph; D, endoscopy; E, CT). F, Endoscopic view showing the inside of the PPC through the stent. G, Radiograph showing removal of necrotic tissue by using a basket. H, CT showing complete resolution of the PPC by drainage with the stent.

2) Clinical Study of EUS-guided Transluminal Drainage with AXIOS stent

Shah RJ, Shah JN, Waxman I, et al. Safety and efficacy of endoscopic ultrasound-guided drainage of pancreatic fluid collections with lumen-apposing covered self-expanding metal stents. Clin Gastroenterol Hepatol. 2015 Apr;13(4):747-52

This study was planned to evaluate the safety and efficacy of a lumen-apposing, covered, self-expanding metal stent used for transluminal drainage of pancreatic fluid collections (PFCs) including symptomatic pancreatic pseudocyst (PPs) and walled-off necrosis (WON).

AXIOS stent, the lumen- apposing, covered, self-expanding metal stent (LACSEM), was inserted in 33 patients from 7 institutions at an average age of 53 years diagnosed of pancreatic pseudocysts with a size of more than 6 cm containing a fluid content of 70% and walled-off necrosis (WON). Cystoenterostomies were created based on endoscopist preference.

The mean size of the patients' PFCs was 9±3.3 cm. LACSEMSs were placed successfully via endoscopic ultrasound guidance in 30 patients (91%, 30/33); the remaining 3 patients received plastic stents. One subject could not be evaluated because of a pseudoaneurysm. In the patients receiving LACSEMS, PFCs resolved in 93% (27/29). Overall, PFCs resolved in 91% (30/33). Endoscopic debridement through the LACSEMS was conducted in 11 subjects. Complications occurred in 15%, including 3 patients with abdominal pain, each 1 patient with stent migration, back pain, access site infection, and stent dislodgement.

In conclusion, a lumen-apposing, covered, self-expanding metal stent (LACSEMS) was safe and efficient for pancreatic fluid collections (PFCs) drainage in this study. Advantage of the LACSEMS over other stents include single-step deployment and the ability to perform endoscopic debridement of necrotic tissues with minimal stent migration.

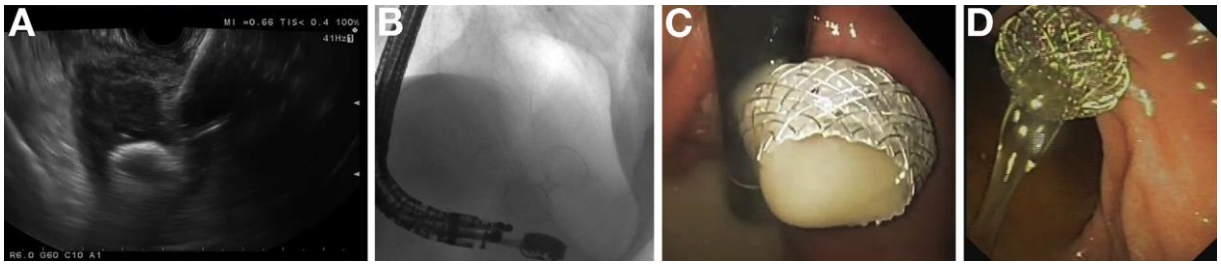


Figure 1. (A) Endoscopic ultrasound showing needle puncture of the pancreatic pseudocyst. (B) Fluoroscopic image showing fully deployed LACSEMS. (C) Endoscopic image showing pus draining through the LACSEMS. (D) Endoscopic image showing pancreatic pseudocyst fluid drainage through the LACSEMS.

6.3. Investigational Device

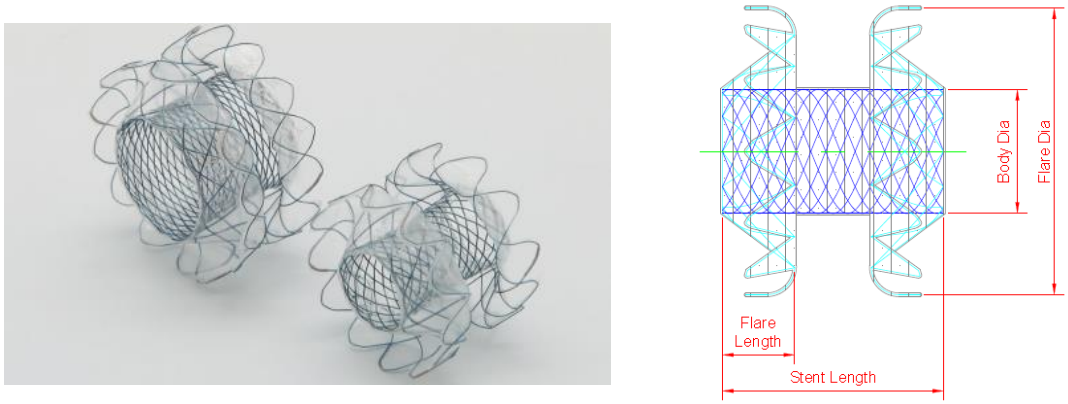
- Product Name : Niti-S SPAXUS^{TM} Stent
- Manufacturer : Taewoong Medical Co., Ltd.
- Item Classification : Orthopaedic materials [B03000]
  As a newly developed medical device, there is no designated subcategory

6.3.1. Composition of the Medical Device

The investigational device 'Niti-S SPAXUS^{TM} Stent' is used for drainage of cystic fluid by being connected to the pancreatic pseudocyst through human organs such as stomach or duodenum. It is composed with a stent made of nitinol and introducer system. The stent has a self-expandable structure in which the shape memory alloy wires made of nitinol are woven into a cylindrical mesh. The stent is designed to confirm the position of the stent as coated with a silicone membrane on the surface and insertion of a platinum marker.

The introducer system consists of two shafts. The proximal portion of the inner shaft is made of stainless steel and the distal and outer sheaths are made of thermoplastic material. The median inner diameter of the inner shaft is connected to the distal tip, and a guidewire (Optimos^{TM} Guidewire, TaeWoong Medical Co., Ltd.) is placed through the median inner diameter to pass through the inner lumen. In addition, a blue zone is added to the outer sheath of this product to allow identifying the movement during the stent deployment on the endoscope. A tungsten x-ray marker is inserted into the 1st inner sheath which enables the expansion of the stent can be confirmed through the fluoroscope. The stent was also made of nitinol wires and a platinum marker is inserted to confirm the position of the inserted stent.

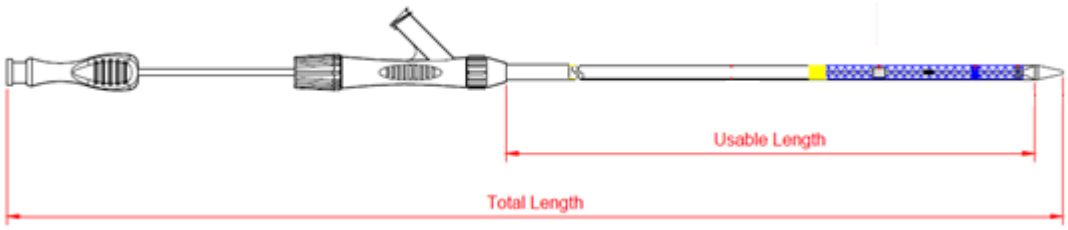
The following describes the dimensions and names of the Niti-S SPAXUSTM Stent and Introducer system model name.



<Figure 1. Dimensions of the Niti-S SPAXUSTM Stent & Introducer system by Model Name >

Art. No.	Body		Flare	
	Diameter (mm)	Length (mm)	Diameter (mm)	Length (mm)
SS0802FW	8	20	23	6.5
SS1002FW	10	20	25	6.5
SS1602FW	16	20	31	6.5

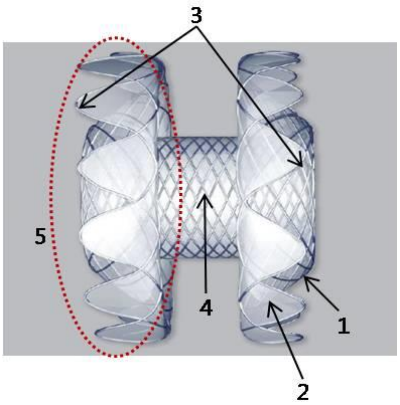
※Allowable Error: Stent ±5%



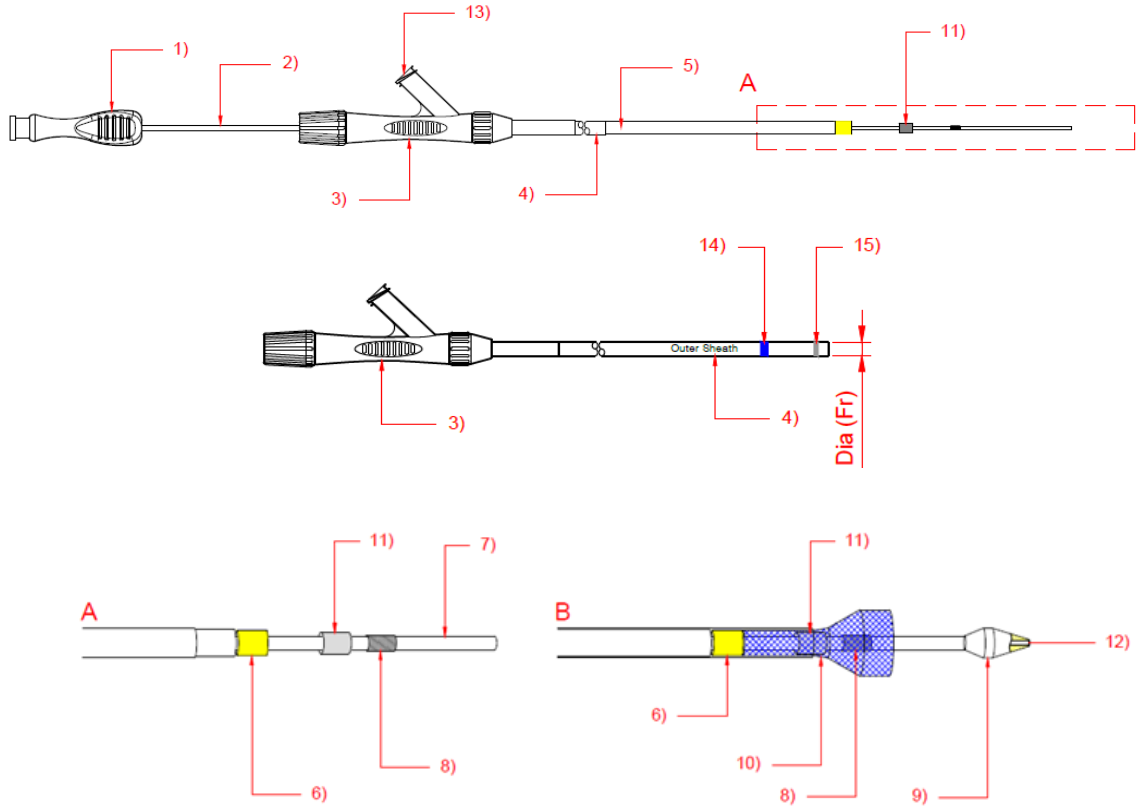
Art. No.	Outer Diameter (mm)	Usable Length (cm)	Total Length (cm)
SS0802FW	3.3 (10Fr)	180	204
SS1002Fw			204
SS1602FW			206

※Allowable Error: Introducer system ±10%

<Figure 2. Part names of the Niti-S SPAXUS™ Stent & Introducer system>



No.	Part Name	Function
1	Stent Body	Consisted of Nitinol wire
2	Cover membrane	Prevents leakage and facilitates removal with silicone coating
3	Platinum Marker	X-Ray marker that identifies the stent position
4	Connector tube	Prevents Nitinol wire loosening
5	Flare	Prevents stent migration



No.	Part Name	Function
1	Hub	Pass the guidewire through the inner diameter
2	Pusher	Irrigation through the side hole
3	Y-Connector	Deliver the supporting force to stent when pulling the outer sheath during deployment of the stent
4	Outer Sheath	Block the expansion of the stent
5	2nd Inner Catheter	deliver the force of pusher to the stent
6	Yellow Marker of Inner Diameter	Identify the location under the endoscope
7	1st Inner Catheter	Pass the guidewire through inner diameter
8	Center X-Ray Marker	Identify radiation-opaque locations
9	Tip	Reduce resistance when progressing along the guidewire
10	Stent	Restore the expansion of stenosis
11	Holder	Anchoring of stent
12	Hole	Hole for passing of the guide wire
13	Side Hole	irrigation
14	Blue zone	Confirmation of stent deployment
15	Distal X-Ray Marker	Identify radiation-opaque locations

6.3.2. Instruction for Use

Endoscopic Ultrasound should be performed to determine the extent and shape of the lesion prior to stent insertion.

1) Determination of Stent Size

① The length and diameter of the stent should be determined by the investigator after endoscopy and / or fluoroscopy.

② The length and diameter of the stent should be selected so that the walls of the two penetrating organs are at the closest proximity to each other so that it can be prevented from migration.

2) Preparation of Stent Deployment

① Under endoscopic ultrasound guidance, a transluminal puncture is performed using a conventional endoscopic instrument (e.g. a fine-needle aspiration needle) in accordance with the preference of the investigator who operates the intervention, avoiding the blood vessels crossing at the position closest to the target pseudocyst.

② Introduce the guidewire (Optimos™ Guidewire, TaeWoong Medical Co., Ltd.) through the lumen of the needle which is used for puncturing into the target pseudocyst sufficiently, and remove the needle while leaving the guidewire in the cyst.

③ After removal of the needle, insert an dilating device such as a cystotome (or needle knife) and/or a balloon catheter along the guidewire until it is progressed across the lesion.

④ After dilating, carefully remove the dilating device.

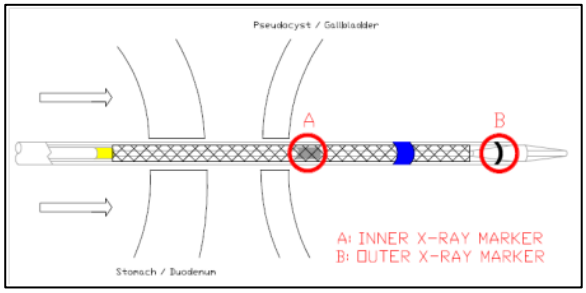
⑤ Remove the stylet from the distal end of the introducer system.

⑥ Ensure that the valve of Y-connector connecting the inner sheath and outer sheath is locked by rotation proximal valve end in a clockwise direction to prevent premature stent deployment.

3) Stent insertion method

Caution: Twisting or turning the introducer system during deployment can affect misplacement and stent performance

① Place the introducer system under the guidance of fluoroscopy and / or endoscopic ultrasound. The internal X-ray marker ('A') must pass through the wall of the pancreas or gallbladder.



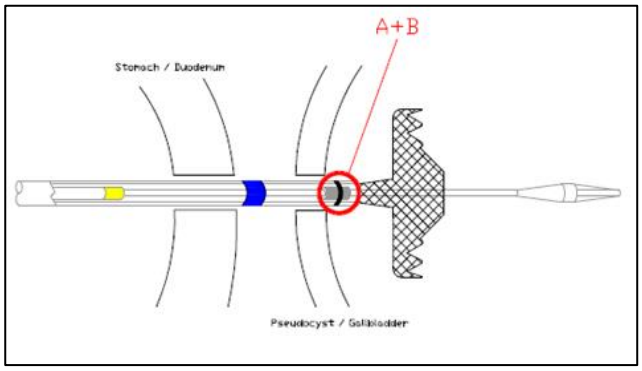
② If the introducer system is located at the correct position, confirm whether the valve of the Y-connector is loosened by turning it counter-clockwise.

③ To begin stent deployment, immobilize the hub in one hand and grasp the Y-connector with the other hand. Gently slide the Y-connector back along the pusher towards the hub

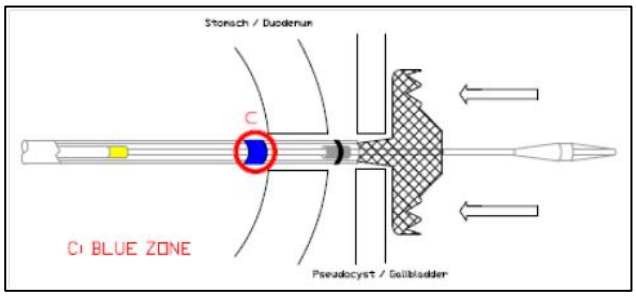
④ Under EUS and fluoroscopic guidance, the distal flare is deployed inside of the target site

➔ Slowly pull back the Y connector when the outer X-ray ring overlaps with the x-ray marker on the inner sheath

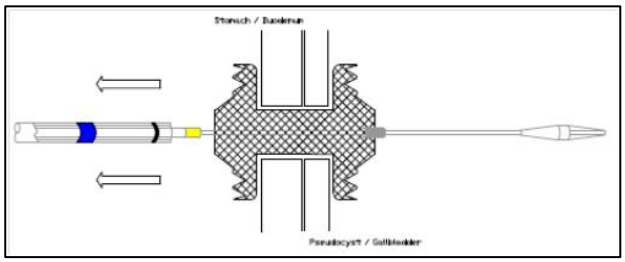
➔ Check the opening of the distal flare.



⑤ Pull back the entire delivery system till seeing the blue marker of outer sheath under endoscopic view



⑥ Deploy the proximal flare of the stent under endoscopic guidance while making sure that the stent connects both walls together.



Caution: Do not push forward or pull backward on the hub with the stent partially deployed. The hub must be securely immobilized. Inadvertent movement of the hub may cause misalignment of the stent and possible damage.

4) After insertion of the stent

① Use a fluoroscope and an endoscope to confirm the expansion of the stent.
② Carefully remove the introducer system, guidewire and endoscope from the patient. If excessive resistance is felt during removal, wait 3~5 minutes to allow further stent expansion. (Place the inner sheath back into the outer sheath as the original state prior to removal)
③ Depending on the judgment of the investigator, the balloon dilatation inside the stent can be performed.

5) Routine procedures after insertion of the stent

① Assess the good position of the stent and effective drainage. A Stent may require up to 1 to 3 days to expand fully.
② It is possible to prescribe appropriate medication for each patient in accordance with the experience and decision of the investigator.
③ After the stent is implanted, a soft diet should be given according to the investigator's decision.
④ Observe the patient for symptoms of any complications.

6) Instruction for removal of the Niti-S SPAXUS™ stent
Remove the stent with forceps or snare carefully and smoothly.

6.3.3. Storage Method and Expiration Date

1) Storage before use

Store at 10 to 40 ℃ avoiding direct sunlight

2) Storage after use

The introducer system and the removed stent should be classified as the in-hospital medical waste and disposed after use in accordance with relevant laws and regulations since they are disposable items.

3) Expiration date
The items are valid to use for 2 years from the date of manufacture.

6.3.4. Purpose of Use of Investigational Medical Device

This investigational device is intended for the drainage of pseudocyst by connection to the pancreatic pseudocyst through adjacent organs such as stomach or duodenum.

7. STUDY OBJECTIVE

This study was planned to confirm the effectiveness and safety of 'Niti-S SPAXUS^{TM} Stent', a lumen-apposing, fully covered, self-expandable metal stent, being used for EUS-guided transluminal drainage for the treatment of pancreatic pseudocyst.

The primary objective is to assess whether the size of the pancreatic pseudocyst is reduced by more than 50% after the intervention to confirm the clinical effectiveness of the Niti-S SPAXUS^{TM} stent.

The secondary objective is to evaluate the incidence and mean of the followings to determine the effectiveness and safety of the Niti-S SPAXUS^{TM} stent.

- Technical success
- Stent lumen patency
- Stent removal success
- Procedure time
- Procedure / Device related serious adverse events
- Other adverse events

8. EXPECTED STUDY PERIOD

It is expected that the study implementation will take about 15 months after the approval of the clinical investigation plan obtained from the Ministry of Food and Drug Safety and the IRB, including 12 months for the subject enrollment period and 3 months for the follow-up period at maximum. Afterwards, it will take about 3 months for data processing, statistical analysis and preparation of the clinical study report additionally.

- Subject recruitment: 12 months
- Follow-up observation period: 3 months
- Data processing and statistical analysis: 2 months
- Preparation of the clinical study report: 1 month

9. SUBJECT SELECTION AND SAMPLE SIZE

9.1. Subject Selection

9.1.1. Inclusion Criteria

Patients who meet all of the following inclusion criteria may be enrolled in this study.

① Male and female adults over 19 years of age

② Patients diagnosed with pancreatic pseudocyst who satisfy the following criteria and who

require the drainage treatment.

- When the size of the pseudocyst is 6 cm and larger (based on the maximum cross-sectional area on CT)
- When the fluid content of the pseudocyst is more than 70%
- When the pseudocyst is in a position to allow transluminal drainage

③ When the patient is willing to participate in the clinical study complying with treatments and procedures, and to visit the hospital for all follow-up evaluations.

④ When the patient heard a description of the purpose, method and effectiveness of this clinical study and has voluntarily signed a written informed.

9.1.2. Exclusion Criteria

Patients who meet any item of the following exclusion criteria will not be enrolled in this study.

① When the patient cannot use appropriate contraception as a woman of childbearing age, or when the patient is pregnant or breastfeeding

② When the patient is not possible to undergo the endoscopic intervention

③ When an effective drainage is difficult due to severe septation in pseudocysts

④ When the patient is severely allergic to contrast agent and Nitinol, etc

⑤ When the patient has a hemorrhagic disease or coagulation disorder (e.g. DIC)

⑥ When the platelet count is less than 60,000 cells/mm^3 or exceeds the International Normalized Ratio (INR) 1.5

⑦ When the patient has hemodynamic instability (e.g. shock)

⑧ When the patient has immunosuppressive diseases such as malignant tumors and bone marrow transplantation, or is receiving immunosuppressive treatments such as chemotherapy or immunosuppressive drugs

⑨ If the patient has any active infectious disease requiring antibiotic treatment, such as known or suspected meningitis or endocarditis

⑩ If the patient has any psychiatric illness or conditions that makes participation in the clinical study impossible (e.g. dementia, seizure)

⑪ If the patient has participated in other clinical studies for medicines or medical devices within the last 3 months

⑫ When the investigator determines that the Niti-S SPAXUSTM Stent procedure is not possible for the patient

9.2. Estimation of Sample Size and Rationale

This clinical study is a single-arm study to evaluate the effectiveness and safety of the Niti-S SPAXUS^{TM} stent for the treatment of pancreatic pseudocysts. The primary effectiveness endpoint is the clinical success rate at the time point of stent removal (Day 30 or 60). It is the clinical success rate.

This study aims to evaluate the effectiveness of the Niti-S SPAXUS^{TM} stent by confirming its non-inferiority through comparing the clinical success rate of the investigational device with the reference value of minimum effectiveness.

The hypothesis of this study is as follows.

$$H_0: P_1 - P_0 \leq -\delta \quad vs \quad H_1: P_1 - P_0 > -\delta$$

The number of subjects calculated using the sample size derivation equation is 31 subjects, and a total of 35 subjects will be recruited in this clinical study, taking the withdrawal rate 10% into account.

< Sample Size Calculation Equation >

$$\mathrm{n} = \frac{\left(Z_\alpha + Z_\beta\right)^2 p_1 q_1}{(\epsilon - \delta)^2}$$

- Significance Level: 2.5%, one-tailed test
- Statistical Power : 80%
- p_1: Clinical success rate of the investigational device 96%
- p_0: Clinical success rate expected from previous studies 96%
- q_1: $1 - p_1$
- ϵ: $p_1 - p_0$
- δ : Non-inferiority margin (0.10)

<Rationale for establishing clinical success rate and non-inferiority limit>

The clinical success rate at the time point of stent removal is reported 86.2% according to the approval data of the commercially available AXIOS stent submitted to the US FDA. The clinical success rates of EUS-guided transluminal drainage using a lumen-appending stent were 93.3% (29 cases), 100% (8 cases) and 100% (7 cases) respectively in the studies performed afterwards by Shah RJ (2015), Gornals JB (2012) and Moon JH (2014). The weighted average calculated for each study was about 96%, which was established as the expected clinical success rate of this study.

< Weighted average equation >

$$\frac{93.3 ation\ ve 8 + 100 \times 7}{29 + 8 + 7} = 95.58 \approx 96$$

Regarding the non-inferiority margin, the clinical success rate was reported to be between 71% and 100% in the existing studies performed in the pancreatic pseudocyst, which means the variability of the treatment effect when using the stent. It was within the half of the effectiveness range 29% presented by the existing studies, and the non-inferiority margin was established as 10% considering the opinions of the investigators and the clinical significance.

<Table 1. References for sample size calculation>

No.	References	Clinical Success Rate (%)	Number of Cases
1	Shah RJ (2015)	93.3%	29
2	Gornals JB (2012)	100%	8
3	Moon JH (2014)	100%	7
4	Talreja JP (2008)	78%	18
5	Cahen D (2005)	71%	92

1) Shah RJ, Shah JN, Waxman I, et al. Safety and effectiveness of endoscopic ultrasound-guided drainage of pancreatic fluid collections with lumen-apposing covered self-expanding metal stents. Clin Gastroenterol Hepatol. 2015 Apr;13(4):747-52

2) Gornals JB, De la Serna-Higuera C, Sánchez-Yague A, et al. Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent. Surg Endosc. 2013 Apr;27(4):1428-34.

3) Moon JH, Choi HJ, Kim DC, et al. A newly designed fully covered metal stent for lumen apposition in EUS-guided drainage and access: a feasibility study (with videos). Gastrointest Endosc. 2014 Jun;79(6):990-5.

4) Talreja JP, Shami VM, Ku J, et al. Transenteric drainage of pancreatic-fluid collections with fully covered self-expanding metallic stents (with video). Gastrointest Endosc. 2008 Dec;68(6):1199-203

5) Cahen D, Rauws E, Fockens P, et al. Endoscopic drainage of pancreatic pseudocyst: long-term outcome and procedural factors associated with safe and successful treatment. Endoscopy. 2005 Oct;37(10):977-83.

10. STUDY METHOD AND PROCEDURE

10.1. Study Design

The study is designed to be conducted as a prospective, multi-center, single arm, non-inferiority, open-label study to confirm the effectiveness and safety of the Niti-S SPAXUS^{TM} Stent, being used for EUS-guided transluminal drainage in patients with pancreatic pseudocyst. It will be performed in a total of 35 patients at 6 institutions.

10.2. Observation Items · Clinical Lab Test Items and Observational Test Method

10.2.1. Laboratory tests

The laboratory tests will be carried out at every visit from the baseline (within 7 days of the procedure), and the following items will be included.

- Hematological test : CBC, WBC differential count
- Blood Coagulation Test : PT, aPTT, INR
- Serum chemistry test : Total bilirubin, Direct bilirubin, AST, ALT, Alkaline Phosphatase, γ-GT, glucose, Amylase, Lipase, CRP
- Pregnancy Test : The pregnancy will be tested at the baseline (within 48 hours of the procedure) in women of childbearing ages, using a urine test (or β-HCG) for confirmation

10.2.2. Clinical symptoms

The clinical symptoms will be checked at every visit from the baseline and the following items will be included as the pancreatic pseudocyst-related symptoms.

- Abdominal Pain
- Nausea
- Vomiting
- Anorexia
- Diarrhea
- Others (e.g. fever, a tender mass in abdomen)

10.2.3. Radiological Examination (X-ray)

X-ray (abdomen) will be performed at baseline, on the day of procedure (Day 1), on the following day of procedure (Day 2), at Discharge (Day 5 ± 2 days), and at Day 20 after stent removal, and the following items will be evaluated by the investigator.

- Location and status of the stent
- Presence/absence of the stent fracture
- Presence/absence of the stent migration

10.2.4. Abdominal CT Scanning

The abdominal CT scanning will be conducted on the baseline and at the time point of the stent removal (Day 30 and/or 60), and the following items will be evaluated by the investigator.

- Size of the pancreatic pseudocyst
- The extent of Fluid content contained in the pancreatic pseudocyst

10.2.5. Endoscopy

This will be performed at the time point of the stent removal (Day 30 and/or 60) and the stent lumen patency will be evaluated by the investigator.

10.3. Study Methods

10.3.1. Screening /Baseline

<Visit 1>

Among patients diagnosed with pancreatic pseudocysts via abdominal ultrasonography, endoscopic ultrasound, abdominal computed tomography (CT), or magnetic resonance imaging (MRI), those who are required to undergo the EUS-guided transluminal drainage will be referred to this clinical study. After the patient heard a description of the purpose, method and effectiveness of this clinical study and has voluntarily signed a written informed consent, when the patient satisfies the inclusion • exclusion criteria, will be enrolled to this clinical study from implementation of the following procedures as specified in the clinical study schedule, and will be assigned with the subject identification code.

The following procedure will be performed during screening / baseline visit.

- Demographics and Physical Measurement (Date of birth, Gender, Alcohol drinking, History of smoking, Height and Weight)
- Vital Signs (Blood pressure, Pulse rate, Respiration rate, Body temperature)
- Physical Examination
- Medical History / Allergy (Significant past medical and surgical History, Current medical history, Medications and Other allergies)
- Laboratory tests (Hematology, Coagulation, Chemistry, and Pregnancy Test for women at childbearing age)
- Clinical symptoms
- Radiological Examination (X-ray: abdomen)
- CT Scanning (abdominal CT)
- Concomitant Medications /Procedures

10.3.2. Day of Procedure

< Visit 2>

Subjects who meet all criteria for the inclusion • exclusion will be admitted to the hospital on the day before the procedure in accordance with the clinical standard of the institution and will undergo the EUS -guided transluminal drainage using the SPAXUS stent. The following procedure shall be

performed on the day of the procedure and the subject should be stay in the hospital for at least one day or more after the procedure for observation of the progress.

- Vital Signs (Blood pressure, Pulse rate, Respiration rate, Body temperature)
- EUS-guided transluminal drainage with Niti-S SPAXUS^{TM} Stent
- Laboratory tests (Hematology, Coagulation, Chemistry)
- Clinical symptoms
- Radiological Examination (X-ray: abdomen)
- Concomitant Medications /Procedures
- Adverse Events /Serious Adverse Events

10.3.3. Follow-Up Observation

< Visit 3>

After the procedure of the Niti-S SPAXUS^{TM} Stent, the subjects will be observed for the post-procedure treatment and progress in accordance with the clinical standard of the institution. On the following day of the procedure (Day 2), the investigator will confirm the location and deployment state of the stent and the stent lumen patency through clinical symptoms, laboratory tests and radiological examination, and evaluates the clinical symptoms and the adverse events. Then, the following procedures will be performed.

- Vital Signs (Blood pressure, Pulse rate, Respiration rate, Body temperature)
- Physical Examination
- Laboratory tests (Hematology, Coagulation, Chemistry)
- Clinical symptoms
- Radiological Examination (X-ray: abdomen)
- Concomitant Medications /Procedures
- Adverse Events /Serious Adverse Events

< Visit 4>

Subjects enrolled in this study will have a follow-up visit at the time of discharge (Day 5 ± 2 days) and the following procedures will be performed at the visit.

- Vital Signs (Blood pressure, Pulse rate, Respiration rate, Body temperature)
- Physical Examination
- Laboratory tests (Hematology, Coagulation, Chemistry)
- Clinical symptoms
- Radiological Examination (X-ray: abdomen)
- Concomitant Medications /Procedures
- Adverse Events /Serious Adverse Events

< Visit 5>

At Day 30 (± 10 days) after the procedure, abdominal CT scanning will be performed to confirm the resolution of the pancreatic pseudocyst which is the primary effectiveness endpoint of the study, and to assess the clinical success. If the subject meets the criteria for stent removal through such as laboratory tests, clinical symptoms and abdominal CT scanning by the judgement of the investigator, the stent will be removed using an endoscope and the following procedures will be performed.

- Vital Signs (Blood pressure, Pulse rate, Respiration rate, Body temperature)
- Physical Examination
- Laboratory tests (Hematology, Coagulation, Chemistry)
- Clinical symptoms
- CT Scanning (abdominal CT)
- Removal of Niti-S SPAXUS^{TM} Stent (using endoscopy)
- Evaluation of clinical success
- Evaluation of the stent removal success
- Concomitant Medications /Procedures
- Adverse Events /Serious Adverse Events

< Visit 5-1>

If the subject fails to meet the criteria for stent removal at Day 30 after the procedure, the procedure the investigator will evaluate whether the stent is removable through the laboratory tests, clinical symptoms, and abdominal CT scanning at Day 60 (± 10 days) after the procedure. If the drainage is not achieved sufficiently at Day 60 after the procedure and the placement of the drainage tube is required (e.g. untreated pancreatic pseudocysts communicated with the main pancreatic duct), the Niti-S SPAXUS^{TM} stent will be removed and a plastic stent will be inserted. The following procedures will be performed.

- Vital Signs (Blood pressure, Pulse rate, Respiration rate, Body temperature)
- Physical Examination
- Laboratory tests (Hematology, Coagulation, Chemistry)
- Clinical symptoms
- CT Scanning (abdominal CT)
- Removal of Niti-S SPAXUS^{TM} Stent (using endoscopy)
- Evaluation of clinical success
- Evaluation of the stent removal success
- Concomitant Medications /Procedures
- Adverse Events /Serious Adverse Events

< Visit 6>

At Day 20 (± 10 days) after removal of the stent, an evaluation of the investigational device and the procedure-related adverse events will be performed and the following procedures will be performed.

- Vital Signs (Blood pressure, Pulse rate, Respiration rate, Body temperature)
- Physical Examination
- Laboratory tests (Hematology, Coagulation, Chemistry)
- Clinical symptoms
- Radiological Examination (X-ray: abdomen)
- Concomitant Medications /Procedures
- Adverse Events /Serious Adverse Events

10.3.4. Concomitant Therapies

All medical devices (e.g. plastic stent) and medications that may affect the effectiveness or safety of the investigational device are prohibited. Prophylactic antibiotics will be administered according to the clinical standard of the institution, and the post-procedure administration of all conventional drugs such as analgesics and digestive agents is allowed. All drugs taken prior to the enrollment in the clinical study due to underlying diseases and any additional drugs added after the Niti-S SPAXUS^{TM} stent implantation should be recorded in the case report form.

10.4. Subject Identification Code

The patients determined as confirming to the inclusion • exclusion criteria after giving the written informed consent to participate in the clinical study, will be enrolled in this study. The subjects enrolled in the study will be assigned with the subject identification code sequentially, and they will be given a total of four digits including the 2 digits of the institution number in order of 01, 02, 03 and etc.

e.g. | **0** | **1** | **-** | **0** | **2** | The subject's identification code of the 2nd enrollment subject from the first institution.

11. STUDY EVALUATION

The primary and secondary effectiveness assessments will be conducted by the investigator based on the results of clinical symptoms, laboratory tests, endoscopy, X-ray and abdominal CT scanning.

11.1. Effectiveness Assessment

11.1.1. Effectiveness Endpoints

1) Primary Effectiveness Endpoints
- Clinical success

2) Secondary Effectiveness Endpoints
- Technical success
- Stent lumen patency
- Stent removal success
- Procedure time

11.1.2. Effectiveness Assessment Criteria and Methods

1) Primary Effectiveness Assessment

■ Clinical success

When the size of pancreatic pseudocyst confirmed by abdominal CT at Day 30 or 60 (± 10 days) after the procedure of the Niti-S SPAXUS™ stent is reduced by 50% at least compared with the baseline, it will be evaluated as clinically successful [17].

2) Secondary Effectiveness Assessment

■ Technical success

If the stent is deployed successfully in the gastrointestinal tract and the pseudocyst, and if the drainage is confirmed visually, it is considered technically successful [18].

■ Stent lumen patency

The stent lumen patency will be evaluated by the investigator at Day 30 or 60 (± 10 days) after the procedure of the Niti-S SPAXUS™ stent through clinical symptoms and endoscopy.

■ Stent removal success

When the Niti-S SPAXUS™ Stent is successfully removed by using forceps or snare through endoscopy as the treatment is succeeded clinically at Day 30 or 60 (± 10 days) according to standard procedures and the criteria for stent removal are met, it is considered as the stent removal success. At Day 30 after the procedure, if the investigator determines that the removal criteria are not met and that a further stent drainage is necessary, the possibility of stent removal at Day 60 (± 10 days) after the procedure is evaluated again and the Niti-S

SPAXUS™ Stent will be removed at the time point. However, if sufficient drainage is not achieved even at the maximum of 60 days and a drainage tube (e.g. an untreated pancreatic pseudocyst communicated with the main pancreatic duct) is needed, the Niti-S SPAXUS™ stent will be removed and a plastic stent will be inserted. Plastic stent insertion is not applicable to a clinical success.

Criteria for Stent Removal

The size of the pancreatic pseudocyst is reduced to 3 cm or less based on the maximum cross-sectional area on the CT or the time point of 60 days after stenting [17)]

- Procedure time

  The time is measured from the moment that the endoscope is inserted into the oral cavity to the time point at which the endoscope is removed.

11.2. Safety Evaluation

11.2.1. Safety Evaluation Variables

- Procedural / Device related SAEs
- Other adverse events

11.2.2. Safety Assessment Criteria and Methods

- Procedural / Device related SAEs

  The incidence of serious adverse events related to the procedure or the Niti-S SPAXUS™ stent is assessed at Day 20 after the stent removal.

- Other adverse events

  The severity and incidence of all other adverse events than those mentioned above occurring during the follow-up period are evaluated at Day 20 after removal of the Niti-S SPAXUS™ stent.

Independent member (gastroenterologist) unrelated to the implementation of the clinical study will continue to review the safety data. Advisory member may recommend changes to the clinical investigation plan in order to improve the safety of the study subjects, and may recommend the early termination of the clinical study, if there is a serious risk to the safety of the subjects due to the progress of the clinical study. The data safety monitoring results by independent advisory member will be reported to the IRB at the regular / interim or at the study completion reporting.

12. SAFETY ASSESSMENT CRITERIA INCLUDING ADVERSE EVENTS/ ASSESSMENT METHOD AND REPORTING METHOD

12.1. Definition of Adverse Event /Adverse Device Event

① An "Adverse Event (AE)" refers to any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

② "Adverse Device Event (ADE)" refers to any harmful and unintended event caused by or associated with the investigational medical device, which undeniably has the causal relationship with the investigational device.

③ "Unanticipated Adverse Device Effect" refers to any pattern or the risk extent of the adverse device event, which is not consistent in reflection to the medical device related information available such as the description in the investigator's brochure(IB) or the supplementary to the device.

12.2. Definition of Serious Adverse Event /Adverse Device Effect

Serious Adverse Event /Adverse Device Effect refers to the adverse events or adverse device effects occurred due to the investigational device, which is applicable to any of the following consequences.

① Resulted in death or life threatening
② Required inpatient hospitalization or prolongation of existing hospitalization
③ Resulted in persistent or significant disability/incapacity
④ Caused a congenital anomaly/birth defect

12.3. Adverse Event Assessment

12.3.1. Severity Assessment

When an adverse event occurred, it should be reported according to the following severity assessment criteria

① Mild
When the AE easily tolerated and are of minor irritant type causing no loss of time from normal activities (or functions)

② Moderate
When the AE introduce a low level of inconvenience or concern to the participant and may interfere with daily activities

③ Severe
When the AE interrupt the participant's normal daily activities

12.3.2. Assessment of the Causal Relationship with the Investigational Medical Device

A causality for all the adverse events should be assessed by the investigator and properly recorded. Upon the incidence of an adverse event, the investigator shall evaluate the relation with the investigational medical device according to the following criteria.

① Definitely related
② Probably related
③ Possibly related
④ Probably not related
⑤ Definitely not related
⑥ Unknown

12.4. Adverse Event Assessment Criteria

Any undesirable medical findings on the occurrence of symptoms which were not observed before the participation of this clinical study but newly occurred shall be classified and assessed as adverse events. Expected adverse events will be classified the adverse events and the severity of them shall be classified as to mild, moderate and severe. They will be reported by using the terms based on the 'Preferred Term' and the 'System Organ Class' of MedDRA.

12.5. Reporting Method of Adverse Event

12.5.1. Reporting of Adverse Event

The investigator is responsible to make assessment of all adverse events occurring during the clinical study period and to record them in the case report forms. All adverse events are to be analyzed in the clinical study report and will be assessed.

12.5.2. Reporting of Serious Adverse Event · Adverse Medical Device Effect

Upon the occurrence of any serious adverse event/adverse device effect, the investigator is required to record it in the case report form and the serious adverse event/adverse device effect record form provided by the sponsor, and must report it to the sponsor within 24 hours from the time that the incidence has been known, whether or not related to the investigational device.

The sponsor must notify all unexpected, serious device effects to the investigator, the institutional

review board (IRB) (only applicable when the principal investigator did not report to the IRB or when the reported details require changes) and the Minister of Food and Drug Safety within the time periods specified by each section of the followings.

1) Resulted in death or life threatening, the sponsor should report the case within 7 days from the day the fact had been reported or known. However, in such case, the detailed information should be reported additionally within 8 days since the date of initial report.

2) In case of all other unexpected serious adverse device effects, the case should be reported within 15 days from the date of report received or getting to know about them.

When there is any additional information regarding the serious adverse events/adverse device effects reported, the sponsor should keep reporting until the adverse device effect is resolved (referring to the disappearance of the adverse device effect or to the impossible follow-up).

12.5.3. Reporting of Device Deficiencies

All deficiencies of a medical device related to its identity (e.g. label), quality, durability, reliability, safety or performance should be recorded in the investigational product complaint form provided and should be notified to Taewoong Medical Co., Ltd. If any adverse event is occurred in the subject due to device deficiency, the adverse event should be recorded in the case report form.

12.6. Expected Adverse Events and Precautions for Use

12.6.1. Expected Adverse Events

< Expected Adverse Events during the procedures of the Niti-S SPAXUS^{TM} Stent >

- Bleeding
- Stent misplacement
- Inadequate expansion
- Stent migration
- Pain
- Perforation

< Expected Adverse Events after Deployment of the Niti-S SPAXUS^{TM} Stent >

- Bleeding
- Pain
- Perforation
- Stent misplacement
- Stent migration

- Stent occlusion
- Fever
- Pancreatitis
- Abscess formation
- Vomiting
- Pneumoperitoneum
- Intraperitoneal leakage
- Peritonitis
- Hematoma
- Inflammation
- Infection
- Fistula
- Ulceration
- Sepsis
- Rupture of intracystic artery
- Stent removal failure

12.6.2. Precautions for Use of 'Niti-S SPAXUS™ Stent'

1) Contra-Indications

① When the patient has hemodynamic instability
② When the patient has severe coagulopathy
③ Use for the reason other than the indications
④ Recapture during the deployment of the stent

2) Precautions for Use

① The instructions should be read carefully before using this device, and the device should be used and supervised by a trained physician. A careful understanding-in-depth of the techniques, principles, clinical applications and risks associated with the operation of the device is required prior to the procedure.
② Care should be taken for removal of the guidewire and the introducer system while the stent is not being fully deployed immediately after stenting.
③ Care should be taken for expanding the stent after deployment since it may cause perforation, bleeding and stent migration.
④ The device should be used after checking the expiration date specified in the package.
⑤ Fluoroscope is recommended otherwise the stent may be misplaced.
⑥ The expiration date should be checked, and the device should not be used if the expiration date has passed.

⑦ This medical device is supplied as sterilized and should not be used if the package is opened or damaged.

⑧ This medical device shall be used only once as single use devices, cannot be used by re-sterilizing.

⑨ If this device is used for vascular system, the safety and effectiveness of medical device cannot be guaranteed.

⑩ This device requires to take precautions for use, and should be used after fully considering the bleeding frequency, coagulopathy, radiation colitis, and proctitis of the patients.

⑪ In sensitive patients, allergic reaction may be caused by Nickel component of the stent.

⑫ The introducer should not be exposed to organic solvents such as alcohol.

⑬ The device should not be used together with Ethiodol or Lipiodol contrast agent.

⑭ Do not change the position of the stent after complete deployment.

13. CRITERIA FOR STUDY DISCONTINUATION AND DROP-OUT

The clinical study can be discontinued in accordance with the decision of the principal investigator, IRB or any regulatory agency. The subject can be discontinued the participation in the study or dropped out of the study due to the withdrawal of the consent or the safety issues.

13.1. Study Discontinuation

13.1.1. Criteria for Discontinuation

① The investigator may discontinue the clinical study if it is judged that the continuation of the clinical study in the light of the results observed during the clinical study implementation affects the safety of the subject. The principal investigator should notify immediately about this matter to the sponsor, the IRB and the Ministry of Food and Drug Safety, and submit a detailed reason(s) for this action of the study suspension.

② The sponsor can make a decision to discontinue the clinical study for safety concerns or administrative reasons, and should notify the discontinuance to the principal investigator, IRB and the Ministry of Food and Drug Safety with submission of detailed reason(s) in writing for the discontinuance.

13.1.2. Handling of Discontinuation

① If the clinical trial is discontinued, the principal investigator must notify all subjects within 30 days and collect all materials and items. In addition, the principal investigator should summarize the progress status and results of the clinical study and complete the case report

forms of all subjects as much as possible, and then, should return the investigational medical device to the sponsor.

② In the event of the early termination or discontinuation of the clinical study, the principal investigator should notify the study discontinuance in writing to the Ministry of Food and Drug Safety and IRB.

13.2. Study Drop-out

13.2.1. Criteria for Drop-out

① When a subject or legally acceptable representative requests to stop participating in the clinical study

② When a medical device is used or surgery and drug are used in combination which may affect the safety and effectiveness assessments

③ When an adverse event is occurred making the clinical study cannot be no longer carried out because it affects the safety of the subject.

④ When a subject fails to adhere to the details of the subject compliance presented in the informed consent including that the subject refuses to follow the instruction of the investigator, or fails to perform the treatment method adequately, which affect the effectiveness assessment.

⑤ Others such as when the principal investigator determines there is a problem in progressing the clinical study

13.2.2. Handling of Drop-out

① If a subject is dropped out of the study, the reason for drop-out and the clinical study-related records conducted before the drop-out will be recorded and retained.

② If a subject fails to visit the hospital during the clinical study, the reason should be made clear and the subject's condition should be checked.

③ Data of subjects who are dropped out will be included in the effectiveness and safety evaluation analysis unless there is a valid reason or reason.

14. Statistical Analysis

A two-tail test will be performed for statistics at a significance level of 0.05 unless otherwise specified, and the statistical analysis will be done using a statistical package SAS V9.4.

14.1. Assessment Analysis Set

The analysis of clinical success and the effectiveness endpoints will be conducted in FAS as the main analysis population, while the analysis of the safety evaluation variables will be conducted in the Safety Set.

- SS (Safety Set)

  All subjects who attempted to receive the Niti-S SPAXUS^{TM} Stent procedure among those who satisfied the inclusion/exclusion criteria and gave the informed consent for participation in this clinical study.

- FAS (Full Analysis Set)

  Subjects who underwent the Niti-S SPAXUS^{TM} Stent procedure and completed the primary effectiveness assessment among those who satisfied the inclusion・exclusion criteria and gave the informed consent for participation in this clinical study.

- PP (Per Protocol) Set

  Subjects who have completed the study with no serious violation of the clinical investigation plan among those who satisfied the FAS.

  Serious clinical investigation plan violations

  - When a subject did not perform the treatment method properly
  - When medical devices, surgery, or drugs that may affect the safety and effectiveness assessments for the investigational device, are used in combination

14.1.1. Effectiveness Assessment Analysis Set

The effectiveness assessment analysis is performed in FAS as the main analysis group. In other words, the analysis will be performed in the subjects who underwent the Niti-S SPAXUS^{TM} stent and have the results of effectiveness assessment at the time point of the stent removal among those who satisfy the inclusion • exclusion criteria, consented to participate in the clinical study. However, analysis in the PP set will be also carried out and the results will be compared.

14.1.2. Safety Evaluation Analysis Set

The safety evaluation analysis is conducted in the Safety Set.

14.2. Statistical Analysis Method

14.2.1. Analysis of General Matters

In case of continuous variables with regard to the demographic and the clinical characteristics of the subjects, the descriptive statistics (number of cases, mean, standard deviation, median value, minimum and maximum values) are presented, whereas in case of categorical variables, the frequency and the percentage are presented. For the variances of continuous data, Paired t-test or Wilcoxon's signed rank sum test will be conducted whereas for the variations of categorical data, McNemar's test will be conducted.

14.2.2. Analysis of Effectiveness Assessment

14.2.2.1. Analysis of Primary Effectiveness Assessment

The number and percentage of patients who achieved clinical success at the time of stent removal are presented. A one-sided 97.5% confidence interval is to be calculated to confirm the degree of non-inferiority for the reference value (96%) and the difference (Investigational device - reference value) and if the lower limit of the confidence interval is -10% or higher, the non-inferiority will be considered to be confirmed.

14.2.2.2. Analysis of Secondary Effectiveness Assessment

Regarding the secondary effectiveness variables, for categorical data, the frequency and percentage as well as 95% confidence interval will be presented. For continuous data, descriptive statistics (number of cases, mean, standard deviation, median value, maximum and minimum values) are provided

- Technical success
- Stent lumen patency
- Stent removal success
- Procedure time

14.2.3. Analysis of Safety Evaluation

The safety evaluation variables such as the frequency and percentage of stent rupture, re-operation, reoperation, procedure or medical device related serious adverse events and deaths are presented, and a summary by each subject is described.

The descriptive statistics (number of cases, mean, standard deviation, median value, maximum and minimum values) are presented for the continuous variables such as all adverse events, vital

signs, and physical examinations collected from the subjects. The changes of post-stent application compared to pre-stent applications will be analyzed by using Paired t-test or Wilcoxon signed-rank test for continuous variables, and McNeamar's test for categorical variables. The adverse events are classified by using MedDRA and these cases are reported using 'Preferred term' and 'System organ class'. All adverse events are presented by the frequency (percentage) by subjects and the number of subjects. When calculating the subject frequency, if multiple cases of same adverse event occur in one subject based on 'Preferred term' and 'System organ class', it will be considered as one case. Whereas the severity and the causality differ for the same adverse event, it will be processed as the maximum severity and causality. The total number of subjects is used in calculating the subject percentage, and when calculating the number of cases, the case like the one mentioned above will be regarded as different adverse events.

For subjects experiencing the adverse event (or adverse device effect) at least one or more, the subject frequency and percentage will be presented and also a 95% confidence interval will be provided. In addition, for the serious adverse events and the subjects dropped-out of the study due to them, the frequency and percentage of subjects should be presented and listed.

14.2.4. Statistical Processing of Missing Data

For the effectiveness endpoints, no separate correction of missing data will be performed because the subjects whose effectiveness assessment is not performed are not to be included in the analysis according to the definition of the main analysis set. Also in the case of safety evaluation variables, the raw data shall be used as they are without any missing value correction.

15. POLICIES ON THE SAFETY PROTECTION OF THE SUBJECTS

15.1. Investigator

The investigator should inform the subject or the regally acceptable representative about the nature of the clinical study, its purpose, implementation procedures, expected benefits and discomforts as well as adverse events sufficiently before obtaining the informed consent of subjects for participation in the clinical study and must provide the subjects full information in a written form of "Subject Information Sheet". In addition, the investigator must give ample time and opportunity for the subject or the subject's legally acceptable representative to inquire about the details of the clinical study and to make decision for participation in the study, and the investigator should answer all the questions related to the clinical study faithfully.

15.2. Institutional Review Board (IRB)

The investigator must obtain prior approval from the IRB for the clinical investigation plan, the informed consent form, the subject recruitment advertisement and other related documents if applicable before starting the clinical study. All correspondence with the IRB and authorizations should be kept in the investigator's site file.

In the event of changes requiring the approval of the IRB and the Ministry of Food and Drug Safety, the changes made will not apply prior to obtaining the approval of the IRB on the revised clinical investigation plan, revised informed consent form, and other relevant documents. However, the amendment of the clinical investigation plan to eliminate the obvious and immediate risks to the subject can be applied immediately prior to the approval of the IRB.

15.3. Subject Informed Consent

The investigator should obtain the informed consent of subjects, by complying with the ethical principles and standards based on the Declaration of Helsinki. Prior to the beginning of the clinical study, the investigator should have the IRB approval of the written informed consent form, the subject information sheet and other documented information to be provided to subjects.

The investigator must give ample time and opportunity for the subject or the subject's legally acceptable representative to inquire about the details of the clinical study and to make decision for participation in the study, and the investigator should answer all the questions related to the clinical study faithfully.

Prior to participation in the clinical study, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the investigator who obtains the informed consent. In addition, the investigator should provide the subject's legally acceptable representative with a copy of the signed and dated informed consent form prior to participation in the clinical study. If the format of the consent form is changed during the clinical study, the investigator should give a copy of the changed consent form to the subject or the subject's representative. If there is a change in the document information already provided to the subject, a copy of the applicable changed document must be provided.

15.4. Agreement of Compensation for Victims

If the subject is injured by the use of the investigational device or clinical study procedure by participating in the trial, the subject will be treated according to the clinical standard care of the hospital and will be charged for the treatment in accordance with the Agreement of Compensation for Victims and the policy of the clinical study insurance taken out by the sponsor.

15.5. Medical Care of the Subjects after the Study

The subjects will be followed-up in accordance with the clinical standard of the hospital after the completion of this study. When the subject is dropped out of the study or has any remaining symptoms of the adverse events even after the completion of the study, the subject will be examined and treated until the symptoms of the adverse events are completely resolved, in accordance with the clinical standard of the hospital.

16. OTHER REQUIREMENTS FOR THE SAFE AND SCIENTIFIC CONDUCT OF THE STUDY

16.1. Management of the Investigational Device

16.1.1. Management and Labeling of the Investigational Device

The principal investigator and the investigational device manager of the applicable institution are responsible to manage the investigational device. The investigational device should be stored in compliance with the conditions designated by the sponsor and the relevant laws and regulations. The investigational device manager must implement the work affairs such as receipt of the device, inventory management, and supply and return of the device by subject, and should record relevant matters and inform the principal investigator on regular basis.

The investigational device manager should keep the records of the investigational device application period, its lot number or serial number, shelf-life or expiration date, the device identification code and the subject identification code by subject. In addition, the investigational manager must maintain the medical records by which whether the application to each subject is conducted in accordance with the instruction for use described in the clinical investigation plan can be confirmed. Also, the manager must confirm whether the inventory of the investigational device is consistent with the record of use.

The items to be listed on the investigational device are as follows.

① Indication of “For clinical trial use only”
② Product Name and Model Name
③ Batch number or Lot number and Date of Manufacture (YY/MM/DD) or Expiry date
④ Storage (Retention) Method
⑤ Name of Manufacture or Importer
⑥ Statement as “It cannot be used for any other than the investigation”

16.1.2. Return and Disposal of the Investigational Device

When the investigational device should be returned, or disposed for reasons such as failure of the investigational device, completion of the clinical study (including early termination) or due of the expiration date, the investigational device manager must record it in accordance with the relevant procedures and returns the device to the sponsor.
The sponsor shall dispose of the returned devices in accordance with the relevant regulations, and shall prepare and keep a record concerning the disposal of the investigational device.

16.2. Confidentiality

The investigator shall keep all information related to the investigational device and the clinical study as confidential, except when requested by the subject, the relevant laws or regulations, the IRB or the regulatory authority. Records that can disclose the identity of subject must be guaranteed for anonymity, and all records of the subject's identity should be kept confidential, even when the results of the clinical study are published. The monitoring personnel and the auditor of this clinical study can have a direct access to the subjects' records for the purpose of monitoring, auditing, and managing the progress of the clinical study.

The investigator should be aware that by signing the contract of this study, the monitor and the auditor of this clinical study can review or copy the applicable documents to verify the medical records and the records in the case report form of the subject. The principal investigator must keep the confidentiality of this information and must be equipped with facilities and management standards for confidential retention. All documents related to the clinical study, such as the case report form, should be recorded and classified with the initials of subject and the subject identification code rather than the subject's name.

16.3. Protocol Compliance and Amendment

The principal investigator should conduct the study in compliance with the description in the clinical investigation plan, and if any clinical investigation plan deviation is required, it should be reported to the IRB.

When the clinical investigation plan requires any amendment, it must obtain the approval of the IRB and the approval of the Ministry of Food and Drug Safety as necessary. In addition, the investigator should not apply any changed contents of the clinical investigation plan before obtaining the approvals of the IRB and the Ministry of Food and Drug Safety, except where necessary to eliminate an immediate hazard(s) to the study subjects. If the changed details of the clinical investigation plan are applied before obtaining the approvals of the IRB in order to eliminate an immediate hazard(s) to

the study subjects, the investigator must submit the changes to the IRB (for post approval) and the Ministry of Food and Drug Safety (when required according to the relevant regulations) as promptly as possible. And documents approved by the IRB chairman or administrator should be retained.

Significant amendments of the clinical investigation plan include addition of safety information, changes in the clinical study procedures, changes in the inclusion and exclusion criteria of subjects, changes in endpoints, and changes in the number of subjects. These changes must be approved by the Ministry of Food and Drug Safety and should be documented and retained.

16.4. Monitoring

The principal investigator should establish a monitoring plan in consideration of the purpose and complexity of the clinical study and the number of subjects, and thoroughly check the progress of the clinical study. The monitoring is conducted in order to protect the rights and welfare of the subjects, to verify the accuracy, completeness, and verifiability of the data through a comparison of the reported clinical study related data with the source documents and to verify that the clinical study is performed in accordance with the clinical investigation plan and the relevant laws and regulations including the standard operating procedures (SOPs), the Medical Devices Act, ICH-GCP and ISO14155.

The monitoring will be conducted by monitors appointed by the sponsor through visiting the institutions and the phone calls. During the monitoring visit, the monitors should confirm the maintaining of the clinical study data such as the original subject record, the investigational device management record, and the investigator’s site file (ISF), and verify the progress of the clinical study and its related records. To do this, the principal investigator should provide the monitors a direct access to the source documents of the subject (e.g. medical record, laboratory test results) and inform any issues occurred in the course of the clinical study implementation to the monitors with full co-operation for the monitoring activities. The monitors should discuss and communicate findings detected during the monitoring procedures with the investigator.

16.5. Data Processing and Storage

16.5.1. Case Report Form

All information related to clinical study should be recorded in the source documents. In most cases, the source document is the subject's medical record, and the information collected in the case report form should be consistent with these medical records. The case report form should be prepared by the investigator or authorized responsible person. If any revision occurs in the case report form, a single line should be drawn on the record, and the initials of the person who makes the revision, date and reasons of revision should be written, and the original entry details should be confirmable.

The investigator should allow direct access to the source document and the case report form at the time of monitoring, auditing, IRB review, and inspection of the regulatory authorities related to the clinical study. The completed case report form will be retrieved by the sponsor and its copy will be kept in the institution. The case report form prepared should not be provided to any third party without the agreement of the sponsor for any reason or in any form, except for the representative authorized by the sponsor or the regulatory authorities.

16.5.2. Storage of the Study Data

The investigator should keep the data related to this study without any damage or loss maintaining the security for the longest period among the times specified in the ICH-GCP, the clinical study contract, relevant laws and regulations, or in the sponsor's SOP. If the investigator is unable to keep the clinical study related records for any reason during the required period, it should be notified to the sponsor in advance. The applicable clinical study data should be transferred to the appropriate delegators, including another investigator, another institution or the sponsor. After compliance of the storage period, the agreement of the sponsor should be obtained before disposing of the data.

16.6. Disclosure of Clinical Study Results

All data produced by this clinical study are proprietary to the sponsor and any information related to the clinical study or its results should not be disclosed without written approval from the sponsor.

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Appendices

Appendix 1. Names and Positions of Principal Investigator and Co-investigator

Appendix 2. Name and Position of Monitoring Staff

Appendix 3. Agreement of Compensation for Victims