DE NOVO CLASSIFICATION REQUEST FOR ENDOROTOR®

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Endoscopic pancreatic debridement device. An endoscopic pancreatic debridement device is inserted via an endoscope and placed through a cystogastrostomy fistula into the pancreatic cavity. It is intended for removal of necrotic tissue from a walled off pancreatic necrosis (WOPN) cavity.

NEW REGULATION NUMBER: 21 CFR 876.4330

CLASSIFICATION: Class II

PRODUCT CODE: QNE

BACKGROUND

DEVICE NAME: EndoRotor

SUBMISSION NUMBER: DEN200016

DATE DE NOVO RECEIVED: March 31, 2020

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INDICATIONS FOR USE

The EndoRotor device is indicated to resect and remove necrotic tissue in symptomatic Walled off pancreatic necrosis /Walled off necrosis (WOPN/WON) after having undergone endoscopic ultrasound (EUS) guided drainage.

LIMITATIONS

The sale, distribution, and use of the EndoRotor device are restricted to prescription use in accordance with 21 CFR 801.109.

The device is not intended for uses other than that described in the labeling.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The EndoRotor ® is a powered resection tool intended to morcellate necrotic pancreatic tissue through the instrument biopsy channel of an endoscope. The device is to be used after a patient has undergone a procedure to drain any fluid accumulated in the pancreas due to pancreatitis.

There have been two versions of the device with 510(k) marketing clearance. Version 1 (K170120) was indicated to resect and remove residual tissue from the peripheral margins following EMR (Endoscopic Mucosal Resection). The subject device is identical to Version 2 (K181127). In Version 2 of the device, the sponsor made some minor design changes to the device (described below), and added the post-endoscopic mucosal resection (EMR) tissue persistence with a scarred base to the indications for use.

As shown in Figure 1, the device is composed of the:

1. Power Console
2. Foot Control
3. Resection Catheter (with XT Tip)
4. Specimen trap with pre-loaded filter (not pictured)

Figure 1. EndoRotor Device and its components. 1. Power Console , 2. Foot Controls. 3. Resection Catheter (XT Tip).

The Power Console includes the drive motor, vacuum control valve and a peristaltic irrigation pump, which provides the controls and positive function indicators

The Foot Control is an actuator that enables and disables EndoRotor functions during the procedure.

The Resection Catheter is a disposable component that includes inner and outer debriding cutters (as pictured above). The Catheter can be used to perform lavage and aspiration from the site through the endoscope biopsy channel to the EndoRotor Specimen Trap. The Resection Cutter is available in various sizes and is compatible with various endoscope models as described below (Table 2). In Version 1 of the device, the Resection Catheter had a 3.0 mm^2 window; in Version 2 of the device, the window was 4.4 mm^2. In addition, Version 1 of the device only had an inner cutter, whereas Version 2 of the device had both an inner and outer cutter. Other device specifications were similar.

The Specimen Trap is used for the collection of the resected tissue and is used in procedures for colon or esophagus. The Specimen trap is left empty for DEN procedures.

Table 1 describes the specifications of the EndoRotor device:

Table 1. EndoRotor specifications (Version 2)

Device Specification	Attribute
Window Size	4.4. mm^2
Cutter Design	Inner and Outer Cutters
Operating Speed	High : 1750 RPM Low : 1000 RPM
Flow Rate	5 mL/min
Vacuum	50-432 mmHg (facility regulated vacuum)
Operating Environment	Temperature 15- 40 °C (60 – 100 °F) RH 10-95% Pressure 500 – 1060 kPa
Transport and Storage Environment	Catheter Storage Room Temperature Transport: 29 – 60 °C and 30% to 85% RH Console Storage and transport: - 40 °C to +70 °C 10-95% RH, 500 to 1060 kPa Pressure
Size	Console D: 25.72 cm x W 18.42 cm x H 33.65 cm

Weight	Console Weight: 6.17 kg

Table 2. EndoRotor catheter sizes and compatible gastroscopes for the necrosectomy indication only (Version 2)

Catheter (diameter = 3.2 mm)		Compatible Endoscope(s)*
SKU #	**Working Length (mm)**	***All endoscopes shall have a working channel diameter ≥ 3.2 mm**
ER 10-03-OP-S	1240	Olympus gastroscopes with 1030 mm working length Pentax gastroscopes with 1050 mm working length
ER 10-03-F-S	1270	Fuji gastroscopes with 1100 mm working length
ER 10-01-OP-S	1890	Olympus colonoscope with 1680 mm working length Pentax colonoscope with 1700 mm working length

To use the EndoRotor device, first, a cystogastrostomy is performed, in which a transluminal conduit is created between the pancreas and the stomach or duodenum, and is typically held . with a luminal apposing metal stent (LAMS). Necrosectomy may be performed two days following the placement of the stent, according to the assessment of the treating physician. On the day of the necrosectomy procedure, an endoscope is then advanced into a transluminal cystogastrostomy. Once the endoscope passes the transluminal orifice and the first resection area is identified, the EndoRotor Console is brought to a functional state. The setup process includes the following:

- Powering on the console, placing the foot pedal into position, unpacking and attaching the appropriate EndoRotor Catheter and catheter lock;
- Connecting the proximal connections of the EndoRotor Catheter to the EndoRotor Console;
- Preparing the lavage fluid for use.

Once all set up steps have been fully executed, the physician inserts the selected EndoRotor Catheter into the working-channel of the selected scope. Lavage fluid flow, cutting tip rotation, and aspiration are initiated using the foot pedal.

When the EndoRotor is operational, and vacuum actuated, the physician resects and removes tissue by placing the cutting surface against the necrotic tissue. The user makes small sweeping movements followed by slight articulation of the endoscope to reposition the device for optimal tissue removal as needed. When resecting tissue, the system connects to an in-suite vacuum that

is controlled by a user actuated pinch valve, restricting vacuum to on demand . to suction material from the procedure site through the catheter and back to the specimen trap.

After the procedure is completed, the EndoRotor Catheter is removed and discarded; the console and foot control are cleaned/stored per the instructions for use.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The device components of the EndoRotor (Version 2) device were evaluated according to the FDA guidance (2016), "Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process," and the ISO 10993-4:2017, "Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood." From the evaluations and supporting information, the components of the device were found to be biocompatible for its use.

SHELF LIFE/STERILITY

The EndoRotor Catheter is a sterile, single use system. The catheter component is a single use device provided sterile to the end user. Device components in contact with blood were also tested for pyrogenicity using the USP Chapter <151> Pyrogenicity Test method.

Sterilization methods for the EndoRotor device have been validated in accordance with ISO 11135-1:2007 "Sterilization of Health Care Products- Ethylene Oxide – Part 1: Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices," to ensure a sterility assurance level of 10^{-6} before the device is marketed.

Accelerated aging to support a 2-year shelf life was performed for the EO sterilized EndoRotor device per ASTM F1980-07, Standard Guidance for Accelerated Aging of Sterile Medical Device Packages. The expiration date of 2 years was verified by demonstrating package integrity through dye penetration and bubble leak testing on the stored products. Version 1 of the device was tested and was found to be sufficient for the 510(k) clearance of Version 2.

PERFORMANCE TESTING - BENCH

Non-clinical performance data was generated to mitigate the risk associated with the failure of the device components and/or materials. Functional and torque testing were conducted on Version 2 of the device, to evaluate the critical functions of the device (including device power testing, ability to prime the device, ability to use the device with foot controls, ability to use the irrigation pump, and the ability to torque the device) as well as design verification/validation testing.

PERFORMANCE TESTING – ANIMAL TESTING

Animal testing was conducted for Version 1 of the device (K170120). Version 1 of the device was cleared to resect and remove tissue from the peripheral margins following EMR (Endoscopic Mucosal Resection). The animal testing conducted was deemed to be sufficient for the 510(k) clearance of Version 2 of the device.

No additional animal testing was conducted for Version 2 for the subject indication.

SUMMARY OF CLINICAL INFORMATION

There were three sources of data for this submission: The main source of data was an Investigational Device Exemption (IDE) study, G180127, approved by FDA. There were two additional sources of supporting data: The Erasmus Study, conducted in the Netherlands, and Real World Evidence (RWE), provided by the firm with data obtained from institutions that use the device for the indication of walled off pancreatic necrosis, outside the US. A literature search was also used to assess compare current treatment options with the subject device.

Investigational Device Exemption, G180127:

The EndoRotor DEN trial was a single arm, prospective study to demonstrate the safety of the EndoRotor device for Direct Endoscopic Necrosectomy (DEN). The study was a multicenter and multinational trial, with ten centers. Thirty-seven subjects were consented and screened for symptomatic pancreatic necrosis due to acute pancreatitis. These subjects were assessed to see if they had an indication to undergo endoscopic necrosectomy after having undergone EUS-guided drainage. There were 7 screen failures, and 30 subjects treated with the device. Twenty three out of 30 (77%) subjects were treated in U.S. centers. A single patient was unable to finish the study questionnaire due to a death as discussed below. Subjects could have multiple EndoRotor procedures; there were a total of 63 procedures in this study.

The primary endpoint evaluated device safety. Secondary endpoints evaluated device and procedure effectiveness by assessing the following: 1) successful debridement of at least 70% necrosis by volume measured with a high-resolution, contrast -enhanced CT (CECT) at a 21 (± 7) -day follow up after the last DEN procedure was performed, 2)assessment of total procedure time to achieve clearance of necrosis for all procedures, 3)assessment of adequacy of debridement, 4) assessment of total number of procedures to achieve clearance of necrosis, 5)assessment of length of hospital stay and utilization, and 6) quality of life (SF-36 questionnaire). FDA considered the most objective endpoints for its regulatory decision- making process; that is, those with the least amount of confounding variables (Please see Effectiveness section for additional information.)

Prior to treatment with the EndoRotor device, subjects underwent either traditional cystogastrostomy with balloon dilation or cystogastrostomy via the FDA-approved LAMS, and they must have continued to remain symptomatic following EUS-guided drainage. Symptomatic necrosis caused by necrotizing pancreatitis was first determined by imaging such as CECT showing impaired pancreatic perfusion and then symptoms such as the presence of intolerable pain was confirmed. To confirm the presence of infection, a positive culture obtained by fine needle aspiration (FNA) was required. The protocol required investigators to use the Atlanta

Classification in the determination of all necrotic collections on CECT. To be included in the study, the collection had to have greater than 30% necrosis content and a diameter at least 6 cm and not more than 22 cm. Infected necrosis was suspected in necrotizing pancreatitis subjects with clinical signs of persistent sepsis or progressive clinical deterioration despite maximal support in the intensive care unit (ICU) without other causes for infection. Exclusion criteria included but were not limited to documented evidence of pseudoaneurysm and intervening varices. Seven of the 37 consented subjects did not meet these screening criteria.

Subjects were treated with the device following cystogastrostomy creation and /or at least two days following the time of LAMS placement. According to the protocol, subjects could receive a maximum of 4 EndoRotor procedures. A minimum of 2 days was required between EndoRotor procedures, and all procedures needed to be completed within a 21-day period. Follow-up was completed 21(±7) days after the last EndoRotor debridement, at which time subjects had another contrast-enhanced CT to measure remaining collection volume. At the 21-day follow-up, a physical examination was completed, as well as an assessment of adverse events. Subjects also completed a quality-of-life questionnaire (SF-36).

Erasmus Investigator Study

The Erasmus patient population was a prospectively-defined cohort that followed European Society of Gastrointestinal Endoscopy (ESGE) Guidelines in management of subjects recommended for Endoscopic Transgastric Necrosectomy (ETN)/Direct Endoscopic Necrosectomy (DEN).
Only subjects who met these guidelines were included. The case series was conducted in accordance with good clinical practice (GCP) as described in 21 CFR 812.28(a)(1). Technical feasibility, safety and clinical outcomes were evaluated and scored. . Twelve subjects were treated, 8 of whom were treated with Version 1 of the device, and 4 of whom were treated with the subject version (Version 2) .

Investigators measured effectiveness by recording procedure time and assessing the number of procedures to achieve removal of necrotic tissue. They also tracked adverse events. In the 4 subjects treated with Version 2 of the device, the mean procedure time was 37 minutes (median procedure duration was 33 minutes) the mean number of procedures was 1.75 (the median number of procedures required was 1.5 (range 1 to 3)). Complete removal of necrotic tissue was assessed by visual endoscopic inspection. There were no additional effectiveness data provided in this study, and therefore, FDA did not rely on this study for assessment of the effectiveness of this device. However, FDA did consider this study when evaluating the safety of the device, as is explained further below.

Real World Data
There were two sources of RWD presented to FDA: (1) a systematic review of published clinical studies that evaluated the general safety and effectiveness of DEN procedures and (2) real world clinical data from institutions outside the US that have used the EndoRotor device for treating WOPN. All subjects were treated with Version 2 of the device.

The literature review was conducted according to guidelines and methods suggested by Egger, Smith, and Altman in their book, “Systematic Reviews in Health Care.”

The literature search was conducted for indexed articles using eight query search terms, including broad relevant terms for endoscopic debridement of walled off pancreatic necrosis with current endoscopic accessories/tools (e.g. snares, baskets, balloons, etc.).The scientific literature databases PubMed and Embase were used by the applicant to perform a search for data published through August 23, 2018. The search yielded 520 articles from Pubmed and 2,007 articles from the Embase database, for a total of 2,527 articles.

After elimination of duplicates, the sponsor applied several inclusion and exclusion criteria (e.g. included if the article provided description of clinical trial and results; excluded if clinical data were not extractable for the device in the article, among others).

This narrowed down the search to 28 articles to review. FDA further narrowed these articles by the number of subjects treated per the article (excluded if less than 10 subjects), if the article was a duplicate because it was analyzed in a review article, whether safety and efficacy data were provided in the article for DEN procedures using current endoscopic tools (as opposed to drainage only procedures), and whether the article was a systematic literature search. Therefore, FDA utilized 5 articles to review the safety and effectiveness of current devices used to treat Walled Off Pancreatic Necrosis. It was the intent of FDA to qualitatively compare the data from these 5 articles to the results obtained by the sponsor with the collected clinical trial data discussed within.

For the collection of real world clinical data, Interscope collaborated with 39 sites using EndoRotor as standard of care outside the US. Data were collected for 134 EndoRotor DEN/ETN procedures in 108 subjects.

Data collected included length of hospital stay (LOS), need for multiple interventions, pre and post procedure assessment of percent of necrotic material, adverse events, and serious adverse events. Since the data were not collected as part of a formally designed retrospective clinical study, there were no pre-defined safety or efficacy endpoints.

Efficacy Results

Investigational Device Exemption, G180127:

As stated above, there were several effectiveness endpoints in the study protocol. The following results are addressed below: percent volume reduction, number of procedures, procedure time. Volume reduction is measured at follow-up by contrast-enhanced CT. This was measured by comparing the volume of the WON/WOPN collection calculated from the contrast-enhanced CT performed at baseline and at the 21 (± 7) day follow-up per Table 3.

The sponsor also assessed the EndoRotor procedure time, the adequacy of debridement (endoscopic assessment), the total number of procedures, the length of hospital stay (days), and subject quality of life (SF-36 Questionnaire). These secondary endpoints were not considered by FDA because of confounding variables which were thought to prohibit accurate assessment of outcomes data. For example, the assessment of adequacy of debridement were made via endoscopic visualization after each debridement. Because of potential subjectivity and thus

variability in percentage reduction in cavity size, this data was not considered. However, the CECT evaluations after the final DEN were considered. Finally, the assessment of length of hospital stay (LOS) and utilization, and the quality of life (QOL) SF-36 questionnaire data were not considered due to wide variability in the study subject's disease severity and thus varying LOS and QOL.

As stated above, subjects could receive multiple EndoRotor treatments depending on continued symptomatology (e.g. persistent necrosis, continued fever, sepsis, pain, etc.). Clinicians in the study determined whether additional treatments were required based upon clinical judgement. In this study, 30 subjects received 63 procedures, averaging 2.1 treatments per subject.

Among the 30 subjects who were treated with the EndoRotor (Intent-to-treat (ITT)) population), there were 8 protocol deviations, leading to a per protocol (PP) population of 22 subjects:

- 3 subjects were excluded from the ITT population, because they had more than 4 procedures, based on the clinician's assessment that additional treatment was necessary.

- 5 subjects were excluded from the ITT population, because of the following imaging deviations:

    - 3 subjects received conventional CT without contrast at baseline and 21-day follow-up due to renal insufficiency or contrast allergy.
    - 1 subjects had EUS at baseline and 21-day follow-up
    - 1 subjects had contrast-enhanced CT at baseline and endoscopy at 21-day follow-up in lieu of contrast-enhanced CT

    Although these 5 subjects did not receive contrast-enhanced CT at baseline and follow up, all exams confirmed WON/WOPN resolution, although CECT volume measurements were not available for evaluation.

Table 3 shows the volume reduction results for the 22 PP subjects. As shown in the first row, for the total PP population, the median of the percent reduction of volume was (b) (4)%, which indicates that most subjects experienced more than 98% volume reduction. The range of (b) (4) (b) (4) indicates that at least one patient experienced an increase of volume, but other subjects experienced 100% reduction of volume. The mean percent reduction was (b) (4)%. Eleven subjects had one procedure; 6 subjects had two procedures; 5 subjects had 3-4 procedures. For the ITT population, the results were consistent with the PP population: the median volume reduction was (b) (4)%; the range was (b) (4) %; the mean was (b) (4)%.

Out of the 22 subjects that were included in our PP analysis, 18/22 (82%) had at least a (b) (4)% reduction in their WON size. Out of the 30 subjects that were included in the ITT analysis, there were 24/30 (80%) subjects who had at least a (b) (4)% reduction in the WON Size.

Table 3. Collection Volume at Baseline and 21 Day Follow up, Stratified by the Number of Procedures Required per Patient (Per Protocol, N = 22)

# of DEN Procedures Required per Patient	# of Subjects	Collection Size at Baseline (cm^3) Mean (±SD)	Collection Size 21 days after last treatment (cm^3) Mean (±SD)	% Reduction of WON Size
1-4 (all subjects)	22	(b) (4)		
1	11			
2	6			
3	3			
4	2			

The sponsor also recorded the total procedure time (Table 4), including the debridment time it took for EndoRotor to resect and remove the WOPN/WON. As seen in Table 4, the average time using the EndoRotor device was (b) (4) minutes (standard deviation (b) (4) minutes, range (b) (4) minutes); the average total time needed for the procedure was (b) (4) minutes (standard deviation (b) (4) minutes, range (b) (4) minutes).

Table 4. Total EndoRotor time and Total Procedure Time in up t (b) (4) Procedures. (PP population, N=22)

	Total EndoRotor Time	Total Procedure Time
Mean	(b) (4)	
SD		
Median		
Range		

Real World Data (RWD)

For the collection of real world clinical data, clinicians accessed patient records for routinely recorded information (e.g. procedure time, discharge summary) for subjects who underwent a DEN procedure with the suject device. One hundred and eight records were obtained, in which there were 14 subjects who could not achieve complete WON resolution ((b) (4) %).

(b) (4) subjects had imaging at baseline and a follow up image; 5 out of (b) (4) subjects had an indeterminate number of DEN procedures and were excluded from further analysis. Therefore, (b) (4) subjects were initially included; these pateitns had CECT or MRI scans at baseline and follow up. Twenty nine of (b) (4) patient had a known number of procedures and therefore the sponsor provided FDA an analysis of the data for (b) (4) subjects, stratified by the number of procedures with a cut off of (b) (4) All (b) (4) subjects had (b) (4) or less procedures.

The sponsor also had data for 52/108 subjects (48%), for whom they reported an average length of hospitalization of 31 days (range 0 – 119).

Table 5 below shows the number of subjects requiring up to four procedures, and shows the baseline collection in cm^2 (two dimensional data were collected). Follow up was conducted at several time points (unlike the IDE study that collected data after 21 (±7) days following the last EndoRotor procedure), ranging from 6 to 345 days.

Table 5. RWD Reduction in Collection Size stratified by total procedures required per patient (N=(b) (4)).

# of DEN Procedures Required per Patient	# of Subjects	Collection Size at Baseline (cm^2) Mean (±SD)	Collection Size at follow up(cm^2) Mean (±SD)	% Reduction in WON Size
1-4	(b) (4)			

	(b) (4)
1	
2	
3	
4	

* N/A: Data not available due to a single data point.

Literature Comparison

From the literature search described above, 5 articles were utilized to determine the effectivness of current tools to treat WOPN/WON as shown in Table 6:

Table 6. Effectivness Outcomes Reported in the Literature for current WOPN/WON therapies

Article Reference (Number of subjects)	Number of subjects (in study/underwent DEN)	Percent of subjects achieving Clinical Resolution of pancreatic necrosis*	Mean number of endoscopic procedures needed to resolve pancreatic necrosis.
Puli, 2013	233/233	81.84% (95% CI: 76.73%, 86.44%)	4.09 (95% CI: 2.31, 5.87)

Sharaiha, 2016	124 /78	107/124 (86.3%)	Median 2 (range 1-9)
Gardner, 2011	104 /104	95 /104 (91%)	Median = 3
Thompson, 2015	60/60	86.7%	1.58 ± 0.1 (SD)
Kumar, 2014	24/12	11/12 (92%)	1.4 ± 0.2 (SD)

* Each study had a slightly different definition of "clinical resolution" as described in the text.

As shown in the table above, the effectiveness of current treatment modalites for WOPN/WON varied from approximately 80 – 90%.

The publication from Puli, et al.was a meta-analysis comprising 233 subjects, reported 81.85% of subjects achieved clinical resoluton of their pancreatic necrosis after a mean of (b) (4) procedures. In this article, success was defined as resolution of the necrotic cavity proven by radiology. In one of the articles reviewed in this meta-analysis, Seifert, et al. reported 80% clinical resolution of pancreatic necrosis, with a mean of 6 endoscopic procedures needed to resolve the necrosis.

Sharaiha et al. reported on 124 subjects that underwent endoscopic transmural drainage by using LAMS. The primary outcomes in this article were: 1) rates of technical success (succesful placement of the LAMS), 2) clinical success (resolution of WON, on the basis of image analysis, without the need for further intervention via surgery or interventional radiology). The authors reported that 114 subjects (91.9%) had transgastric drainage of their WON, and 10 subjects (8.1%) had transduodenal drainage. A needle knife or cystotome was used to form a tract in 13 cases. Subsequent DEN through the LAMS was performed in 78 subjects (62.9%). The median number of endoscopic interventions performed (index procedure and subsequent DEN) was 2 (range, 1–9); 30.6% of subjects (n =38) had 1 endoscopic session, 50.8% (n =63) had 2 or 3 sessions, and 18.6% (n =23) had 4 or more sessions to debride the WON. Technical success for placement of the LAMS was achieved in all 124 subjects (100%). Clinical success with successful endoscopic eradication of the WON was achieved in 107 subjects (86.3%); 34 subjects achieved complete resolution of the WON with a single endoscopic session.

Gardner, et al. reported on 104 subjects from 6 participating centers who underwent DEN during the study period. Necrotic pancreatic tissue identified via CT scan was removed by a combination of several endoscopic accesories. This article defined success as resolution or near-resolution (>90%) of cavity without operative or percutaneous drainage of the cavity. In this article, 91.3% (95/104) success rate was reported.

Thompson, et al. reported on 60 consecutive subjects who underwent an average of 1.58 ±0.1 DEN proceduress, with debridement accomplished on the initial procedure in 59/60 (98.3%) subjects In this study the primary outcome was clinical resolution of symptomatic WON after DEN, defined as resolution of primary symptom and absence of abdominal pain, nausea, vomiting, fever, leukocytosis, and sepsis. Clinical resolution occurred in 86.7%, with radiologic confirmation.

Kumar et al. conducted a matched cohort study using a prospective clinical registry. Twenty-four subjects were included. Twelve consecutive subjects from January 2009 to December 2010 were included in the DEN group. Subjects undergoing a step-up approach with primary percutaneous catheter drainage (PCD) were identified from the same registry and matched 1:1 with DEN subjects based on collection size and Charlson Comorbidity Index, a prospectively validated metric. Clinical resolution was defined as resolution of primary symptom and absence of abdominal pain, nausea, vomiting, fever, leukocytosis, and sepsis. The authors reported that 11 of 12 subjects (92%) had clinical resolution of WOPN/WON after DEN versus 3 of 12 (25%) step up approach subjects after drainage ($p<0.01$).

Overall Summary of Effectivness Data

FDA considered two sources of data for its evaluation of effectivness, including an IDE study and Real World Data.

When considering the PP population in the IDE study, the median of the percent decrease from baseline was (b) (4)% (Mean (b) (4)%, Range: (b) (4)% (b) (4)%). Out of the (b) (4) subjects that were included in our PP analysis, (b) (4) (82%) had at least a (b) (4)% reduction in their WON size.

The ITT population had consistent results as the PP population (median reduction of (b) (4)%, mean reduction of (b) (4)%, Range : (b) (4)% (b) (4)%). Out of the (b) (4) subjects that were included in the ITT analysis, there were (b) (4) (80%) subjects who had at least a (b) (4)% reduction in the WON Size.

In this study, (b) (4) subjects received 63 procedures, averaging 2.1 treatments per subject.

In the Real World data, there was a median reduction of (b) (4)%, with an overall mean percent decrease from baseline of (b) (4)% in the size of the WOPN/WON (Range: (b) (4)% (b) (4)%). These two sources of data were sufficient to demonstrate effectivess of the device for the intended use.

The article by Puli, et al. which was a systemic review and meta-analysis of endoscopic transmural necrosectomy (ETN) for walled off pancreatic necrosis, found the pooled proportion of successful resolution of pancreatic necrosis to be 81.84% (95% CI 76.73% to 86.44%). The weighted mean number of endoscopic procedures needed to resolve the necrotic cavity was 4.09 (95% CI 2.31 to 5.87).

FDA considered the decrease in the number of procedures required to treat WOPN as one of the benefits for this device, in addition to providing clinicians a tool specifically indicated for debridement of WOPN.

Safety Results

The following data were presented to FDA for the evaluation of safety of EndoRotor.

Investigational Device Exemption, G180127

Table 7 below shows a summary of the Adverse events seen in the G180127 study.

Table 7. Serious Adverse Events for IDE, G180127

SAE Type	Events(n)	Subjects (n/N) (%)	Procedure Related	Device Related	Time to resolution (days)
Gastrointestinal Bleed	1	(b) (4)	Yes	No	3
	1				4
Pneumoperitoneum ¥	1	(b) (4)	Yes	No	3
Sepsis	1	(b) (4)	No	No	7
Hematemesis	1	(b) (4)	No	No	2
Deep Vein Thrombosis	1	(b) (4)	No	No	24
Pancreatitis	1	(b) (4)	No	No	9
Multiple Organ Failure Syndrome ¥	1	(b) (4)	No	No	N/A
Deaths ¥	1	(b) (4)	No	No	N/A

¥ Pneumoperitoneum, Multiple Organ Failure Syndrome and death occurred in the same patient.

There were 9 Serious Adverse Events, including 3, which were adjudicated as procedure-related (2 gastrointestinal bleeding events and 1 pneumoperitoneum). The patient that experienced a pnuemoperitoneum subsequently had multi-system organ failure that led to death. The patient death occurred approximately 8 days following treatment due to fungicemia and additional persdistent extra-pancreatic fluid collections resulting in shock and multiple organ failure syndrome. There were no device-related SAEs and no Unanticipiated Adverse Device Effects (UADE)

The following definitions for rating severity of adverse events were used:

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

The following non-SAEs took place in G180127 and are categorized by their severity.

Table 8. Non-SAEs, or Unanticipated Adverse Device Effect (UADE) for IDE, G180127. All events were unrelated to device and procedure.

AE Category	AE type	Events(n)	Subjects (n/N) (%)	Severity	Device Related	Procedure Related	Time to Resolution (days)
Gastrointestinal Disorder	Colitis	1	(b) (4) (3.3%)	Mild	No	No	17
	Diarrhea	1	(b) (4) (3.3%)	Mild	No	No	0
	Esophageal Candidiasis	1	(b) (4) (3.3%)	Moderate	No	No	17
Infections	Bacteremia	1	(b) (4) (3.3%)	Moderate	No	No	8
	Clostridium difficile infection	1	(b) (4) (3.3%)	Moderate	No	No	14
Metabolism & Nutrition	Hypokalemia	1	(b) (4) (3.3%)	Mild	No	No	1
	Device Dislocation*	1	(b) (4) (3.3%)	Mild	No	Yes	0
Respiratory & Vascular Disorders	Pleural Effusion	1	(b) (4) (3.3%)	Moderate	No	No	3
	Blood loss anemia	1	(b) (4) (3.3%)	Moderate	No	Possible	**5**
Other	Pyrexia	1	(b) (4) (3.3%)	Moderate	No	No	4
	Insomnia	1	(b) (4) (3.3%)	Mild	No	No	8

*The device dislocation adverse event was due to stent dislodgement. During plastic stent placement and post-debridement, the Investigator dislodged the LAMS. The investigator replaced the LAMS without an additional post-procedure complication.

Erasmus Investigator Study

As stated above, there were (b) (4) subjects treated in total with two device versions; (b) (4) subjects were treated with Version 1 of the device, and (b) (4) subjects were treated with Version 2 of the device. For the evalution of device safety, FDA considered all (b) (4) subjects in the analysis.

The following serious adverse events took place in the Erasmus study:

Table 9. Serious Adverse Events for Erasmus Study

SAE Type	Events(n)	Subjects (n/N) (%)	Procedure Related	Device Related	Time to resolution (days)
Gastrointestinal Bleed	1	(b) (4) (8%)	No	No	6
Multiple Organ Failure Syndrome	1	(b) (4) (8%)	No	No	N/A
Death (Adenocarcinoma Progression)	1	(b) (4) (16%)	No	No	N/A

As per the study, there were no adverse events reported during the necrosectomy procedures or within the next 24 hours. However (b) (4) subjects (27.2%) experienced adverse events within the course of their infected pancreatic necrosis.

- One patient died eight days after the last endoscopic necrosectomy as a result of ongoing multiple organ failure syndrome caused by massive collections of infected pancreatic necrosis which, despite multiple sessions, could not be completely removed.
- One patient was diagnosed with pancreatic cancer three weeks after having undergone two endoscopic necrosectomy (DEN) procedures for infected necrotizing pancreatitis using the EndoRotor and eventually died 3 months after discharge. The patient had numerous CECT scans prior to DEN which did not detect the cancer.
- In 1 patient, a gastrointestinal bleed occurred 2 days after the procedure necessitating coiling of the splenic artery. During the procedure, there was no evidence of bleeding or damage to any exposed vessel in the necrotic cavity.

Since the patient that had an occult cancer was treated with EndoRotor, and subsequently diied of pancreatic cancer 3 months later, as a measure of caution, FDA added a boxed warning to the device labeling. The boxed warning states, "**The EndoRotor device should not be used in patients with known or suspected pancreatic cancer as per the assessment of the treating physician.**"

Real World Data (RWD)

The following Serious Adverse Events were identified from review of the RWD:

Table 10. Serious Adverse Events for Real World Evidence provided to FDA

SAE Type	Events(n)	Subjects (n/N) (%)	Procedure Related	Device Related	Time to resolution (days)
Acute respiratory failure	1	(b) (4) (1%)	No	No	50
Ischemic Stroke	1	(b) (4) (1%)	No	No	N/A
Gastrointestinal Bleed	2	(b) (4) (1%)	No	No	N/A
Multiple Organ Failure Syndrome	2	(b) (4) (2%)	No	No	N/A
Deaths	3	(b) (4) (3%)	No	No	N/A

From the literature search described above, there were five articles that were utilized to determine the safety of current tools to treat WOPN/WON. In general, all articles discussed the procedures for these subjects as first inserting a stent (LAMS or other), and subsequent DEN procedures in a subset of subjects. Because the subject device may also be used with a stent prior to necrosectomy, these articles were thought relevant, as were the Adverse events reported.

The following information was collected (Table 11):

Table 11. Adverse Events and Length of Hospital Stay reported in the literature for current WOPN/WON treatment.

Article Reference (Number of subjects)	Number of subjects in study/underwent (DEN)	Adverse events (Rates or Number of subjects)	Mean Length of Hospital Stay after DEN
Puli, 2013	233	21.33% (95% CI 16.40% to 26.72%) of subjects had • Bleeding • Sepsis • Perforation	32.85 days (95% CI 10.50 to 55.20 days)

Sharaiha, 2016	124/78	<u>(< 30 days): 14 subjects</u> 2 subjects Bleeding 4 subjects Infection 5 subjects Stent Occlusion 3 Stent migration <u>≥ 30 days: 9 subjects</u> 3 subjects Infection 2 subjects Stent occlusion 4 subjects Stent migration	Not reported
Gardner, 2011	104	Complications occurred in approximately 14% of subjects and included • 5 retrogastric perforations/pneumoperitoneum, (managed nonoperatively). • 2 massive bleeding • 4 Infection, bacteremia	12 days (range 9-15 days)
Thomspon, 2015	60	3.3% SAE rate No mortalities	6.8 ±1.0
Kumar, 2014	24/12	1/12 (0.8%) subjects had bleeding	3.0 days

Puli, et al. assessed 233 subjects. Complications were noted in 21.3% of subjects including bleeding, sepsis and perforation. For pancreatic necrosis that did not resolve, surgery had to be performed in 12.98% (95% CI 9.05% to 17.51%) of subjects. The fixed-effect model was used to report all of the pooled proportions.

Gardner et al., 2009 (an article reviewed within Puli et al.) assessed 45 subjects, 25 of whom underwent DEN, and 20 of whom underwent standard endoscopic drainage. The article reported 32% complication rate in the DEN group, but these were limtied to mild periprocedure bleeding, with equivalent rates between groups. The article also reported a mean hospital stay of 15.4 days post-procedures.

Seifert et al. (an article reviewed within Puli et al.) reported 26% complcation rate and a 7.5% mortality rate (93 subjects). The authors also reported an average number of days in the hospital as 46 days (range 8 – 170 days), and the presence of serious complications connected with air embolisms.

Sharaiha et al. reported both short and long term adverse events:

- Short Term (<30 days): Fourteen subjects (11.3%) required re-intervention within 30 days of LAMS placement because of superinfection (n=4), stent occlusion (n= 5), and stent migration (n=3). All migrations occurred during DEN. In all 14 subjects, the initial LAMS was de-occluded, repositioned, or replaced with a new LAMS without significant clinical sequelae. Two subjects developed acute hemorrhage during DEN that required embolization by interventional radiology (IR). There was no procedure-related mortality.

- Long Term (≥30 days): Nine subjects (7.2%) required re-intervention after the first month because of superinfection (n =3), stent occlusion (n =2), and stent migration (n = 4). In all subjects, the initial LAMS was de-occluded, repositioned, or replaced with a new LAMS without significant clinical sequelae. The overall stent migration rate was 5.6% (7). All migrations occurred during DEN.

Gardner et al. (2011) reported 14% of subjects experienced adverse events. There were 5 retrogastric perforations/pneumoperitoneum, (managed nonoperatively), 2 massive bleeds, and 4 infections (bacteremia).

Thompson et al. reported a 3.3% SAE rate. One patient had bleeding that required futher therapy (a hemorrhage during stent deployment that required aniographic emobolization). Another patient with prior attempted surgical necrosectomy experienced capsule perforation during DEN, and was not debrided during the index procedure. The collection was drained and the stomach was endoscopically sutured closed during this index case (the mean DEN procedure time was 83.3.± 7.5 minutes). New endocrine insufficiency was reported in 10% of subjects, and new exocrine insufficiency was reported in 23.3% of subjects.

Kumar et al. reported on twelve consecutive DEN subjects that were matched with 12 step-up approach subjects. Outcomes were clinical resolution after primary therapeutic modality, new organ failure, mortality, endocrine or exocrine insufficiency, length of stay, and health care utilization. DEN resulted in less new antibiotic use, pulmonary failure, endocrine insufficiency, and shorter length of stay ($P < 0.05$). Health care utilization was lower after DEN by 5.2:1 ($P < 0.01$).

Summary of Safety Data

When evaluating the totality of the data, there were five instances of GI bleeding in the three sources of data that were considered SAEs. There were also four episodes of multi organ failure syndrome in the three studies. These were the two most prevalent SAEs that occurred in a total of (b) (4) subjects.

The following table is a summary of the safety data collected from the three sources of data:

Table 12. Summary of Adverse Events reported per source of data

	Erasmus Study (N= 12)	IDE, G180127 (N = (b) (4)	Real World Data (N = (b) (4)
Device Related SAEs	0/12 (25%)	(b) (4) (0%)	(b) (4) (0%)
Procedure Related SAEs	0/12 (0%)	(b) (4) (10%)	(b) (4) (0%)
Not procedure or device related SAEs	5/12 (42%) *Including 2 deaths*	(b) (4) (23%) *Including* (b) (4) *death*	(b) (4) (8.3%) *Including* (b) (4) *deaths*
SAEs requiring surgical intervention	0/12 (0%)	(b) (4) (0%)	(b) (4) (0%)
Unanticipated Adverse Device Effects	0/12 (0%)	(b) (4) (0%)	(b) (4) (0%)

As discussed above, Puli, et al. assessed 233 subjects. Complications were noted in 21.3% of subjects including bleeding, sepsis and perforation. The rate of complications in the subject device was less than compared to current tools used for necrosectomy.

Pediatric Extrapolation

In this De Novo request, existing clinical information was not leveraged to support the use of the device in a pediatric patient population.

LABELING

Labeling has been provided that includes instructions for use and an appropriate prescription statement as required by 21 CFR 801.109. The labeling includes:

- Instructions for Use Manual: The manual is the primary labeling material for the device. It provides information about the device and its components, indications, contraindications, precautions, warnings, possible adverse reactions, device functions, and guidelines for use, including the recommended training for safe use of the device. The manual also includes a summary of the clinical performance testing with the device. Finally, the manual includes instructions and diagrams that explain the steps to prepare the device for use prior to use and explains the steps to resect and remove necrotic pancreatic tissue.

- Package Label: This provides sizing information, manufacturer information, shelf life and product summary.

The labeling includes the following boxed warning: "**The EndoRotor device should not be**

used in patients with known or suspected pancreatic cancer as per the assessment of the treating physician."

TRAINING

Training will be provided to physicians who are clinically trained and experienced in EUS guided drainage and conventional necrosectomy. The goals of the training include:

- A review of the User Manual and discussion of risks and mitigations
- A discussion of previous clinical experience and completed trials
- A discussion on peer reviewed publications
- A review of videos of previous procedures and discussion of best practices
- Proctoring of procedures with Interscope personnel for a minimum of 5 procedures or until the end user demonstrates the ability to perform procedures completely without consultation from Interscope personnel.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of an endoscopic pancreatic debridement device and the measures necessary to mitigate these risks.

Table 13: Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation Pyrogenicity testing
Infection	Sterilization validation Pyrogenicity testing Shelf life testing Package integrity testing Labeling
Electrical shock/electromagnetic interference	Electrical safety testing Electromagnetic compatibility testing
Injury due to device malfunction or device misuse • Injury to pancreas or other non-target tissue • Stent dislodgement	Clinical performance testing Software validation, verification, and hazard analysis Non-clinical performance testing Labeling Training
Injury due to procedure or device	Clinical performance testing Labeling

• Hemorrhage/ GI bleeding • Pneumoperitoneum • Sepsis/multi organ failure • Morcellation of malignant tissue	Training

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the endoscopic pancreatic debridement device is subject to the following special controls:

1. Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including evaluation of debridement of walled off pancreatic necrosis and all adverse events.

2. The patient-contacting components of the device must be demonstrated to be biocompatible.

3. Performance data must demonstrate the sterility of the patient-contacting components of the device.

4. The patient-contacting components of the device must be demonstrated to be non-pyrogenic.

5. Performance testing must support the shelf life of device components provided sterile by demonstrating continued sterility, package integrity, and device functionality over the labeled shelf life.

6. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    a. Testing of rotational speeds and vacuum pressure;
    b. Functional testing including testing with all device components and the ability to torque the device; and
    c. Functional testing in a relevant tissue model to demonstrate the ability to resect and remove tissue.

7. Performance data must demonstrate the electromagnetic compatibility (EMC) and electrical safety of the device.

8. Software verification, validation, and hazard analysis must be performed.

9. Training must be provided so that upon completion of the training program, the user can resect and remove tissue of interest while preserving non-target tissue.

10. Labeling must include the following:

a. A summary of the clinical performance testing conducted with the device;

b. Instructions for use, including the creation of a conduit for passage of endoscope and device into a walled off pancreatic necrotic cavity;

c. Unless clinical performance data demonstrates that it can be removed or modified, a boxed warning stating that the device should not be used in patients with known or suspected pancreatic cancer;

d. The recommended training for safe use of the device; and

e. A shelf life for any sterile components.

BENEFIT-RISK DETERMINATION

There were three sources of data that were provided to FDA for safety and effectiveness data. However, since it was a controlled study, FDA utilized the IDE study only for our benefit-risk determination.

When considering the per protocol population in the IDE study, the median of the percent decrease from baseline was 98.5 for the size of the WOPN/WON (Mean was 82%, range: -9% - 100%). Of the 22 subjects that were included in our PP analysis, 18/22 (82%) had at least a 70% reduction in their WON size.

The ITT population had consistent results as the PP population (median reduction 98.5%, mean reduction 85%, range : -9% - 100%). Of the 30 subjects that were included in the ITT analysis, there were 24/30 (80%) subjects who had at least a 70% reduction in the WON volume.

In this study, 30 subjects underwent 63 procedures, averaging 2.1 treatments per subject.

By means of comparison, the article by Puli, et al. which was a systematic review and meta-analysis of ETN)for walled off pancreatic necrosis found the pooled proportion of successful resolution of pancreatic necrosis to be 81.84% (95% CI 76.73% to 86.44%). The weighted mean number of endoscopic procedures needed to resolve the necrotic cavity was 4.09 (95% CI 2.31 to 5.87). FDA considered the decrease in the number of procedures required to treat WOPN as one of the benefits for this device, in addition to providing clinicians a tool specifically indicated for debridement of WOPN.

In the clinical trial, 3 subjects experienced procedure-related serious adverse events (a 10% complication rate). Two of these subjects experienced gastrointestinal bleeding. The third subject experienced a pneumoperitoneum (air leaking from the pancreatic cavity into the abdominal cavity) and later died after suffering from sepsis and multi-organ system failure caused by massive collections of infected pancreatic necrosis. In the Puli, et al., meta-analysis a 21% complication rate is reported.

The probable risks of the device include the risks associated with an endoscopic procedure, creation of conduit for device passage (such as with a plastic or metal stent), injury due to device malfunction, user error, or risks known to be associated with the EndoRotor DEN such as hemorrhage/thrombosis, pneumoperitoneum, sepsis/multisystem organ failure, and morcellation of malignant tissue.

Clinical trial sample size, protocol deviations, characterization of patient disease severity and outcome, among other considerations, contributed to uncertainty in assessment of benefit-risk. These were considered in light of the potential availability of this first-of-a-kind device indicated for debridement of walled off pancreatic necrosis, as well as the supportive data.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The EndoRotor device is indicated to resect and remove necrotic tissue in symptomatic Walled off pancreatic necrosis /Walled off necrosis (WOPN/WON) after having undergone endoscopic ultrasound (EUS) guided drainage.

The probable benefits outweigh the probable risks for the EndoRotor device. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the EndoRotor device is granted and the device is classified as follows:

> Product Code: QNE
> Device Type: Endoscopic pancreatic debridement device
> Regulation Number: 21 CFR 876.4330
> Class: II

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