ENDOROTOR

Investigational Plan

PROSPECTIVE, RANDOMIZED TRIAL COMPARING THE SAFETY AND EFFECTIVENESS OF THE INTERSCOPE ENDOROTOR® MUCOSAL RESECTION SYSTEM WITH CONTINUED ABLATIVE THERAPY IN SUBJECTS WITH REFRACTORY DYSPLASTIC BARRETT'S ESOPHAGUS

Protocol # CLIN 0010, Revision E, (10 October 2017)

A PROSPECTIVE, MULTI-CENTER, RANDOMIZED TRIAL TO COMPARE THE SAFETY AND EFFECTIVENESS OF THE INTERSCOPE ENDOROTOR® MUCOSAL RESECTION SYSTEM WITH CONTINUED ABLATIVE THERAPY

US FDA IDE # G170106

Sponsor:
Interscope Medical, Inc.
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PROTOCOL SUMMARY

Study Title:	Prospective Randomized Trial Comparing the Safety and Performance of the Interscope EndoRotor® Mucosal Resection System with Continued Ablative Therapy in Subjects with Refractory Dysplastic Barrett's
Protocol No.	CLIN 0010 / D
Study Design:	A prospective, multi-center, randomized trial to compare the safety and performance of the Interscope EndoRotor® Mucosal Resection System in subjects with refractory dysplastic Barrett's Esophagus
Patient Population:	Subjects with refractory Barrett's metaplasia after 3 failed radiofrequency ablations (RFA)
Primary Objective:	To evaluate the EndoRotor®'s ability to completely remove areas of Barrett's metaplasia considered refractory after 3 failed radiofrequency ablations (RFA).
Secondary Objectives:	1. To compare the EndoRotor® to standard of care ablative therapies by determining the percent reduction of activated fibroblasts in the region of resection and ablation, respectively. 2. Assessment of post procedure pain (chest pain discomfort events requiring narcotic analgesic).
Primary Endpoints:	Primary Effectiveness Endpoint: Complete removal of areas of Barrett's metaplasia after no more than two treatments. Primary Safety Endpoint: Assessment of Adverse Events (incidence, relationship to device and severity) compared to the control arm and the medical literature.
Secondary Endpoint:	Percent reduction of the area with Barrett's esophagus that was resected or ablated during the initial treatment session through the final follow-up visits.
EndoRotor® Arm	Once final study eligibility has been confirmed (i.e. after 3 failed radiofrequency ablations (RFA), the patient will receive the EndoRotor® device.
Continued Ablative Therapy Arm:	The EndoRotor® will be compared to continued standard of care ablative therapies with currently available Radio Frequency Ablation (RFA) treatments and/or cryotherapy ablation with cleared cryotherapy devices.
Study Duration:	Subjects will be followed with biopsies of the resected areas at the time of surveillance endoscopies every 3 months until they have 2 consecutive negative endoscopies and biopsies (6 months)
Clinical Sites:	A minimum of 3 and up to 5 sites in the United States will enroll subjects.
Enrollment:	The sites will enroll a total of 120 subjects meeting all inclusion and exclusion criteria to reach a total of 110 evaluable subjects, allowing for 10 subjects lost to follow-up. It is anticipated that there will be a total of 55 evaluable subjects in each arm.

Inclusion Criteria:	1. Subjects who are ≥30 and <79 years of age; inclusive of males and females. 2. Subjects with a history of confirmed Barrett's esophagus with dysplasia (low-grade or high-grade) refractory to radiofrequency ablation 3 times. 3. Residual Barrett's length is ≥1 cm and ≤6 cm. 4. Histologic persistence of intestinal metaplasia (any non-squamous epithelial lesion) following treatment and failed eradication. 5. Following 3 failed RFA procedures with no confirmed evidence of EAC and having confirmed no endoscopic and histologic evidence of EAC at the time of therapy. 6. Subject capable of giving informed consent. 7. Subject has a reasonable expectation for prolonged survival (greater than 5 years). 8. Subject can tolerate repeated endoscopic procedures. 9. Absence of strictures that preclude the passage of the endoscope 10. Subjects with the ability to understand the requirements of the study, who have provided written informed consent, and who are willing and able to return for the required follow-up assessments through 6 months or 9 months, as indicated.

Exclusion Criteria:	1. Subject unable to give informed consent. 2. Subject is unwilling to return for repeated endoscopies. 3. Subject having 3 failed RFA procedures and confirmed endoscopic and histologic evidence of EAC at time of therapy. 4. Residual Barrett's longer than 6 cm. 5. Subjects with nodular Barrett's Esophagus. 6. Subjects who are on aspirin or anticoagulant therapy who cannot stop it and have had bleeding problems during previous endoscopic treatments. 7. Esophageal varices. 8. Active esophagitis. 9. Esophageal stricture preventing passage of endoscope or catheter. 10. Any previous esophageal surgery, except fundoplication without complications. 11. Medically uncorrectable hypotension or hypertension. 12. Any condition that in the opinion of the investigator would create an unsafe clinical situation that would not allow the patient to safely undergo an endoscopic procedure (lack of medical clearance). 13. Pregnant or lactating women or women of childbearing potential who do not employ a reliable method of contraception as judged by the Investigator, and/or are not willing to use reliable contraception for the duration of study participation. 14. Patient has known severe psychiatric disorder, substance abuse, or other reason for being unable to follow trial follow-up instructions. 15. Patient has a known significant concomitant illness with a life expectancy of <1 year. 16. Patient is known to be currently enrolled in another investigational trial that could interfere with the endpoint analyses of this trial.

Primary Analysis:	Per protocol (subjects enrolled in the study and who met all I/E criteria and are treated with the device).
Expected Timelines:	Enrollment: September 2017 – September 2018 Last 6-month Follow-up: February 2019 Last 9-month Follow-up: May 2019 Total Timeline: ~ 21 - 24 months Twelve (12) months to obtain a total of 110 subjects. Subjects who are negative on their surveillance will complete the study in a minimum of 6 months, while those who are positive and require repeat treatment will take 9 months. Those who fail could exit the study between 6 and 9 months after first treatment. The study should be completed between 21 and 24 months after the first subject is treated.
Study Device:	Interscope EndoRotor® Mucosal Resection System
Regulatory Status:	EndoRotor® Mucosal Resection System device is designed and manufactured in the United States for investigational use in the resection of refractory, dysplastic Barrett's esophagus. The FDA cleared the EndoRotor® under the Pre-market Notification, 510(k) program in April 2017 (K170120) for use in endoscopic procedures by a trained gastroenterologist to resect and remove residual tissue from the peripheral margins following endoscopic mucosal resection (EMR). The EndoRotor® is an approved product in Europe having received the CE Mark under MDD 93/42/EEC on Medical Devices Annex II, excluding Section 4.

Study Contacts

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Chief Medical Officer:	Ramon Franco, MD Telephone: 617-872-0128 ramon.franco@interscopemed.com
Device Technical Support	Interscope Medical, Inc. Jeffery Ryan 617-360-1168 Ramon Franco Jr, M.D. 617-872-0128 Normal hours: Mon-Sat 7am to 6pm EST Emergencies (24 hours a day)
Data Monitoring Committee:	An Independent 3-Member Data Monitoring Committee – Members to be selected prior to study initiation
Clinical Research Organization - Study Management, Monitoring, Data Coordination, & Safety/Event Reporting	Alvamed, Inc. Roberta Hines, Acting Director, Regulatory and Clinical Affairs 1116 Great Plain Avenue, Needham, MA, USA 02492 Mobile: 425-766-0308 Fax: 425-974-7915 Email: rhines@alvamed.com

Clinical Investigator Signature Page

The ENDOROTOR Study

Clinical Protocol: CLIN 0010, Version E, "Prospective Randomized Trial Comparing the Safety and Performance of the Interscope EndoRotor® Mucosal Resection System with Continued Ablative Therapy in Subjects with Refractory Dysplastic Barrett's Esophagus – ENDOROTOR". Prior to participation in the ENDOROTOR Study, the Clinical Investigator must obtain written approval from his/her Institutional Review Board (IRB). This approval must be in writing and must indicate the Study name, Protocol number, Institution(s) where the study will be conducted, any local regulations that apply to this trial, and the expiration date of the approval.

By signing below, I confirm that I will not enroll subjects in this study until IRB approval has been obtained at my site. I have signed an Investigator agreement and have completed all of the Sponsor requirements for training on the study and the Interscope EndoRotor® Mucosal Resection System. I have read this protocol and agree to adhere to the protocol and study requirements. I will discuss this protocol and all related study material with the research team at my institution and ensure that they are fully informed regarding the study requirements and use of the EndoRotor® device. I will also ensure that the study is conducted in accordance with all applicable standards and regulations; including, but not limited to, the Declaration of Helsinki, Good Clinical Practices (GCP), FDA IDE regulations (21.CFR.812), the Sponsor, the IRB and any other applicable local or national requirements.

Clinical Investigator

_____ _____

Print Name Signature

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Date (dd/MMM/yyyy)

_____

Institution(s)/Location

1.0 INTRODUCTION & BACKGROUND

1.1 Introduction

The EndoRotor® Endoscopic Mucosal Resection System is an automated mechanical endoscopic mucosal resection system for use in the gastrointestinal tract for benign neoplastic or pre-malignant tissue removal by interventional gastroenterologists and GI surgeons. The EndoRotor® System performs both tissue dissection and resection with a single device through an endoscope's instrument biopsy channel. A motorized rotating cutting tool driven by an electronically controlled console performs tissue resection. Because the system automatically suctions and cuts between 1000 and 1750 times a minute, resected tissue is immediately aspirated away from the resection site and collected onto a micron filter. Tissue collected on the filters can be used for pathological examination using standard methods.

Interscope believes that use of the EndoRotor will allow the elimination of the refractory Barrett's mucosa (epithelium) and the submucosa that contains the activated fibroblasts. Current techniques employ the use of surface ablation with radiofrequency ablation or cryotherapy. Both techniques do not remove the submucosal fibroblasts. A resection technique such as endoscopic submucosal dissection (ESD) is difficult to perform in previously ablated regions due to scar, has a high rate of complications such as perforation and is a lengthy procedure. In Europe, where the EndoRotor® has been used in human cases, anecdotally it has performed well in areas of previous treatment (previous endoscopic mucosal resection - (EMR) with recurrent or persistent lesions in a bed of scar. The EndoRotor's ability to resect the mucosa and submucosa may provide higher rates of complete remission compared to surface-only treatments such as cryotherapy in this patient population.

In this study, Interscope will evaluate the EndoRotor's ability to completely remove areas of Barrett's metaplasia considered refractory after 3 failed radiofrequency ablations (RFA) as compared to continued ablative therapy including radio frequency ablation and/or cryotherapy according to the institutions' standard of care. The study will be conducted at primary referral centers for this patient population.

1.2 Background

Barrett's esophagus (BE) is the only known precursor of esophageal adenocarcinoma (EAC).[(1)] This cancer is one of the deadliest known and affects primarily middle-aged white males. It is estimated by the American Cancer Society that roughly 12,000 individuals will be diagnosed with esophageal cancer in the United States this year, and it is anticipated 11,900 of these individuals will die. Barrett's esophagus has been treated utilizing radiofrequency ablation that produces superficial destruction of the mucosa of the Barrett's segment. Though this is very effective, there is a small but significant number of subjects (8- 10%) who are refractory to therapy, and there is a 5% per year risk of recurrence even after complete ablation.[(2)]

Alternative forms of therapy are available including using widespread mucosal resection and cryotherapy. Widespread mucosal resection is very effective but, unfortunately, has significant complications including a stricture rate in about half of subjects.[(3)] In addition, significant complications such as bleeding and perforation are not uncommon. Cryotherapy may be effective as depicted in case reports.

Currently, researchers hypothesize that individuals who are refractory to therapy may have increased cancer-associated fibroblasts that reside in the lamina propria of the mucosa that are not eradicated by radiofrequency ablation.[(4)] These fibroblasts have become transformed and produce cytokines that increase the likelihood of columnar mucosal regeneration after therapy.[(5)]

1.3 Literature Summary

Although most patients under surveillance for BE do not develop dysplastic tongues or segments, those that do require intervention to avoid progression to EAC. Historically BE patients were treated with endoscopic mucosal resection (EMR) of neoplasia and although EMR produces samples that can be histologically interpreted, a stepwise radical endoscopic resection (SRER) of the Barrett's mucosa is associated with a high stenosis rate of 48%.[3] This directly led to the development of Radio Frequency Ablation (RFA), which utilizes balloons to deliver thermal energy circumferentially to ablating the abnormal lining using radiofrequency energy of superficial BE lesions. More recent developments have narrowed the area of treatment using focal ablation catheters. The use of RFA has shown to be effective in BE eradication typically requiring an average of three treatments with reduced stenosis rates (5%) over EMR but although it is relatively fast and easy to perform, it is expensive (over $2,500 per procedure), it does not harvest tissue for pathological evaluation, and adverse events such as stricture (5%) and bleeding (1%) can occur.[6] A majority of patients will experience chest pain after the procedure which usually lasts a few days, and in 1-2% of patients the pain is more severe and longer lasting.[7,8] Current literature shows up to 10% of patients will continue to develop BE despite 3 separate RFA treatments at which point they are considered refractory.

An alternative technique that has been used is cryotherapy, a technique that delivers extreme cold temperature through a direct spray or via a radial balloon, but this is still a surface ablative therapy. Ablative therapies damage the surface cells creating significant artefact and do not provide histologic specimens potentially hampering decision making and delaying the diagnosis of advanced lesions until they become large enough to be grossly identified. There are limited solutions for refractory BE patients, thus making a clinical rationale to compare the safety and effectiveness of continued ablative therapy to the EndoRotor in a randomized study to salvage RFA failures. In a review of the experience at the Mayo Clinic, Rochester, Minnesota, 46 (18%) patients out of a consecutive cohort of 246 patients treated with radiofrequency ablation of the entire segment still had intestinal metaplasia after three therapies and were classified as refractory. Of these 46 patients, 37 (80%) eventually reached complete endoscopic ablation after a total median of 24 months of therapy (range 14-68 months). In this group, the type of therapy, including cryotherapy, additional radiofrequency ablation, or endoscopic mucosal resection resulted in similar rates of complete response ($p<0.28$). In addition, a recent study was reported by Canto, MI, et. al. on carbon dioxide cryotherapy in a mixed group of primary therapy and rescue therapy for refractory disease. The authors found a complete response of intestinal metaplasia of only 55% in a retrospective cohort of 64 patients at 12 months of initiating cryotherapy.[9]

At the present time, there are no clinical literature reports specific to the EndoRotor® System treating Barrett's esophagus. An investigator-initiated study is underway in the Netherlands evaluating the safety and efficacy of the EndoRotor® in BE in a 30-patient cohort. Additionally, 25 BE patients received EndoRotor treatments to date commercially in Europe. Anecdotally, those patients are reporting pain lasting on average 1-2 days, show no strictures at 3 months and continue to be monitored. Based on extensive pre-clinical and early clinical results in a post-market setting, the EndoRotor® has several inherent advantages over RFA and cryotherapy. It is a mechanical device not functioning in a thermal way delivering neither electrical current nor extreme cold temperature to the lesion. The physician can independently remove mucosa and or sub-mucosa without causing damage or thermal transfer to circular/longitudinal muscle potentially leading to less pain. By not causing damage to muscle it can also

potentially reduce stricture rates. Lastly, the EndoRotor provides histologic specimen, which can be evaluated by a pathologist without thermal artefact. RFA averages $2500 per procedure and 3 procedures per patient ($7,500 - $10,000 total) and cryotherapy costs from $800 - $2000 (varied by supplier). The EndoRotor® costs $600 per procedure; and if capable of eradicating disease in 1-2 treatments, it can be significantly less costly to the healthcare system for BE patients.

2.0 Report of Prior Investigations

2.1 Summary of Prior Human Clinical Use

The EndoRotor® has been used in humans to resect Barrett's metaplasia in 25 BE patients on a post- market basis in Europe and in 11 of 30 patients enrolled in a clinical trial to date. Additionally, the EndoRotor® has been used in 60 patients to treat recurrent colon adenomas in procedures ranging from rectal to cecal lesions.

2.2 Summary of Pre-Clinical (Animal) Testing

Animal testing of the EndoRotor® was conducted to evaluate the overall safety and performance of the device in an animal model. A summary of the study is presented below.

The objectives of this study were to evaluate the EndoRotor® system for performance of tissue resection in an animal model, with respect to safety:

- Assessment of tissue response acutely and at 2 weeks' post-resection utilizing standard light microscopy
- Clinical assessment of bleeding at sites of resection

In addition, the overall performance characteristics of the system were evaluated by multiple operators.

The study was conducted at CBSET in Lexington, Massachusetts, USA as part of a Good Lab Practices (GLP) protocol, as well as for a preliminary research project in Germany at the Institut für Nutztiergenetik, Mariensee, Friedrich-Loeffler-Institut (FLI) Bundesforschungsinstitut für Tiergesundheitusing in live pigs[10]. The animal study was conducted under Good Laboratory Practice (GLP) guidelines. Six healthy, Yorkshire pigs underwent endoscopic procedures. The endoscopic procedure was carried out under general anesthesia with an appropriate endoscope inserted into the rectum and advanced into the colon for treatments, and also into the mouth and advanced into the esophagus and stomach for further treatments. The device was used to perform a series of tissue resections in each animal.

Over 120 resections were completed between the colon, stomach, and esophagus, and distributed across different sizes. Each resection site was scored by the endoscopist for bleeding as mild, moderate, or severe, and at least one resected tissue sample from each organ from each animal collected during the procedures, along with the native colon, stomach, and esophageal sites, were subject to histologic processing (paraffin) and staining (H&E). In addition, on the day the resections were conducted, performance characteristics of the EndoRotor® system were evaluated by two operators (physicians), in accordance with the acceptance criteria of the protocol, covering both performance and intended use.

Perforation and bleeding were the main safety criteria assessed. Other major endpoints were device performance/usability and histopathology. Perforation was noted in 2 (1.6%) of the colon resection sites,

comparing favorably to the published rate of 2.3%. Bleeding was graded as mild (resolves in 2 minutes or less without intervention) in 79.5% of sites, as moderate bleeding (resolves in greater than 2 minutes without intervention) in 19.7% of sites, and one site (0.8% of sites) as severe bleeding (requires intervention to resolve the bleeding) which resolved after epinephrine administration. The bleeding rate that required intervention compares favorably to the rates for current interventional techniques published in the literature (0.8% vs. 1-16%). The study pathologist indicated that use of the EndoRotor® System for mucosal tissue resection in the porcine esophagus, stomach and colon was associated with favorable and clinically acceptable tissue responses. The EndoRotor® System received passing evaluation for all performance and intended use criteria by both physicians for the system usability assessment.

There is one published animal study[4] conducted in Germany. The study performed multiple upper and lower gastrointestinal endoscopic mucosal resections in three healthy live pigs. Animals were anesthetized and kept artificially ventilated while two physicians performed multiple qualitative mucosal resections on various sites of the pigs' esophagus, stomach, duodenum, and colon. Rapid resection of flat and slightly elevated mucosa up to several centimeters in size/diameter was performed. No major bleeding occurred during and after resections. When used properly, no gastrointestinal wall perforations occurred during superficial resections. Perforations in the colon were only observed when the device was deliberately pushed against deeper sub-mucosal layers or when exceptional force was applied to penetrate the gastrointestinal wall. Histologic specimens showed complete mucosal removal at resection sites.

2.3 Summary of Design Verification and Validation Testing

In addition to pre-clinical animal testing, the Interscope EndoRotor® System has undergone extensive design verification and validation testing through a series of physical and mechanical performance tests on the catheter and console. Testing was conducted according to applicable US Food and Drug Administration requirements, requirements of the European Medical Device Directive, applicable ISO standards, and applicable test methods.

Testing of the catheter included sterilization validation with ethylene oxide residuals and pyrogenicity testing as well as biocompatibility testing. Shelf life testing and packaging validation and transport testing was conducted to support a 2-year shelf life for the packaged catheter. These tests included functional and simulated use testing which demonstrated conformance of the product with defined performance criteria out to 2 years.

Design verification testing performed on the console included power up and set up testing, foot pedal controls testing, functional testing, and torque testing. The console was also subjected to electrical safety and electromagnetic compatibility testing as well as evaluated for usability.

Summaries of the design verification and validation testing are provided in the Investigator's Brochure.

2.4 Summary and Conclusions

Review of the prior investigations of the EndoRotor® device demonstrate that the device is biocompatible when utilized as instructed. Bench testing demonstrates that the device meets performance specifications. Pre-clinical and clinical testing performed to date demonstrates that the device is safe and effective in removing mucosal polyps and lesions in both the upper and lower gastrointestinal tract.

3.0 Device Description - Interscope EndoRotor® Mucosal Resection System

The EndoRotor Console® is a reusable device with disposable components (single-use, EndoRotor® catheter). The EndoRotor® cutting device is invasive and is in contact with mucosal membranes for less than 60 minutes. The EndoRotor® is manufactured in several lengths that conform to the lengths of the most popular endoscopes. The FDA cleared the EndoRotor® under the Pre-market Notification, 510(k) program in April 2017 (K170120) for use in endoscopic procedures by a trained gastroenterologist to resect and remove residual tissue from the peripheral margins following endoscopic mucosal resection (EMR). The EndoRotor® was granted the CE Mark in September of 2015.

All investigational devices will have the following label statement: CAUTION – Investigational Device. Limited by Federal law to investigational use.

3.1 Device Components

The Interscope EndoRotor® is a system comprised of the following core components:

- EndoRotor Console®: The system control unit housing the motor drive, peristaltic pump and pinch valve to provide rotation, irrigation, and vacuum regulation respectively. (Figure 1).
- Foot Pedal: Activates/deactivates cutter rotation/lavage and aspiration (suction).
- EndoRotor Catheter: The outer jacket of the cutter catheter serves as the delivery vehicle for the irrigation fluid that flows between the inner wall of the braid and outer wall of the torque coil. It also allows for outer cutter repositioning. The outer braided sheath is attached to the distal cutter at the end of the catheter. The torque coil transmits internal rotation to the inner cutter and is sealed with a shrink sleeve to contain aspiration. The rotation motion cuts tissue, which is simultaneously removed from the resection site by suction. The distal ends of the lavage and aspiration tubing are permanently affixed to the catheter (Figures 2-4).
- Collection Device: EndoRotor Specimen Trap® with pre-loaded micron filter. This custom trap is designed specifically to capture EndoRotor specimen.
- Polyp Filter: Filter Set includes 200 replacement filters that can be exchanged and placed within the EndoRotor Specimen Trap® to ensure collection of resected tissue.

In addition, the device is not user programmable - it utilizes an off-the-shelf Maxon® electric motor built into the console that is not adjustable.

Figure 1. EndoRotor® Console

Figure 2. Tubing and Resecting Cutter Components

Figure 3. Disposable Resecting Cutter

Figure 4. Drawing of Resecting Cutter Deployed in Endoscope Working Channel

3.2 How Supplied

The EndoRotor Console®, power cord, and foot pedal are packaged together and supplied non-sterile. The EndoRotor Catheter is packaged separately, is intended for single use only and is provided sterile. The catheter is sterilized by Ethylene Oxide. The EndoRotor Specimen Trap® with pre-loaded micron filter is provided separately and is supplied non-sterile. Replacement filter sets are sold separately and are also nonsterile.

3.3 Regulatory Status

The Interscope EndoRotor® Mucosal Resection System is for investigational use only in the United States under this clinical protocol. The device is manufactured by Interscope, Inc. in the United States. Interscope has a quality management system in place that is in compliance with the US Food and Drug Administration's Quality System Regulation. The FDA cleared the EndoRotor® under the Pre-market Notification, 510(k) program in April 2017 (K170120) for use in endoscopic procedures by a trained gastroenterologist to resect and remove residual tissue from the peripheral margins following endoscopic mucosal resection (EMR). The EndoRotor® is sold throughout Europe.

3.4 Indication for Use

The Interscope EndoRotor® is intended for use in endoscopic procedures to resect and remove Barrett's esophagus tissue.

3.5 Contraindications

Subjects with endoscopic and histologic evidence of esophageal endoadenocarcinoma at the time of therapy should not be treated with the EndoRotor.

4.0 STUDY DESIGN

4.1 Study Objectives

The primary objective is to evaluate the EndoRotor®'s ability to completely remove areas of Barrett's metaplasia considered refractory after 3 failed radiofrequency ablations (RFA).

Secondary objectives include the comparison of the EndoRotor® to continued ablative therapy by determining the percent reduction of activated fibroblasts in the region of resection and ablation, respectively, and the assessment of post procedure pain (chest pain discomfort events requiring narcotic analgesic) with a 0-10 visual analog pain scale.

4.2 Overview of Study Design

This is a prospective, multi-center, randomized study to compare the safety and performance of the EndoRotor® Mucosal Resection System with continued ablative therapy in subjects with refractory dysplastic Barrett's Esophagus. Subjects must have failed 3 RFA treatments (failure of Barrett's to respond to RFA with a decrease of at least 50% of its length) and following 3 RFA failures have no endoscopic and histologic evidence of esophageal adenocarcinoma at the time of therapy. The subjects are randomized and treated (up to 2 times) with either the EndoRotor® which resects the affected mucosa and submucosa (down to the muscularis propria layer), or with cryotherapy or ablative therapy of the persistent lesions. Subjects will be followed with biopsies of the resected areas at the time of surveillance endoscopies every 3 months until they have 2 consecutive negative endoscopies and biopsies (6 months). Those who are positive after 2 treatments will exit the study and will be deemed treatment failures.

4.3 Primary Endpoints

4.3.1 Primary Effectiveness Endpoint

Complete removal of areas of Barrett's metaplasia after no more than two treatments.

The primary effectiveness endpoint will be measured by post-treatment visual appearance on surveillance endoscopies and the findings on histology from biopsies taken of the treatment site at each endoscopy.

4.3.2 Primary Safety Endpoint

Assessment of Adverse Events (incidence, relationship to device and severity) compared to the control arm and the medical literature.

Adverse events will be compared to the control therapy.

4.4 Secondary Endpoint

Percentage of Barrett's esophagus resected or ablated during the initial treatment session through the final follow-up visits.

The secondary effectiveness endpoint will be measured by post-treatment visual appearance on surveillance endoscopies and the findings on histology from biopsies taken of the treatment site at each endoscopy.

4.5 Clinical Sites & Enrollment

A minimum of three (3) and up to five (5) research sites in the United States will participate in this pivotal study. The sites will enroll a total of 120 subjects meeting all inclusion and exclusion criteria to reach a total of 110 evaluable subjects, allowing for 10 subjects lost to follow-up. It is anticipated that there will be a total of 55 evaluable subjects in each arm. Once the informed consent process is completed and final study eligibility has been confirmed, the patient will have the EndoRotor or continued ablative therapy procedure.

4.6 Study Duration & Follow-Up

Subjects will be followed with biopsies of the resected areas at the time of surveillance endoscopies every 3 months until they have 2 consecutive negative endoscopies and biopsies up to 6 months. Subjects who are negative on their surveillance will complete the study in a minimum of 6 months, while those who are positive and require repeat treatment will be followed to 9 months. Those who fail could exit the study between 6 and 9 months after the index procedure. The study should be completed between 21 and 24 months after the first subject's index procedure.

4.7 Patient Population / Sample Size

Assuming a response rate for Barrett's esophagus with EndoRotor® ablative therapy of 80%, and for cryoablation of 50%, the study will have over 95% power to demonstrate non-inferiority (NI) of EndoRotor® to cryoablation and will have 90% power to demonstrate superiority of EndoRotor® over cryotherapy or ablative therapy using a sample size of 110 evaluable subjects, 55 in each treatment group.

4.8 Subject Recruitment

The subjects will be recruited from the clinical practices of the investigators. Due to the number of recalcitrant Barrett's subjects they follow and are referred each month, there may not be a need to advertise. These centers are major referral centers for advanced cases such as refractory Barrett's esophagus. Subjects

who have failed 3 RFA treatments will be told of the study and asked if they would be interested in participating.

4.9 Subject Screening

Following 3 failed radiofrequency ablations where study eligibility is confirmed, the patient will receive the EndoRotor® device. The patient will be enrolled upon insertion of the catheter into the esophagus. Screening shall include:

- Pregnancy test – within 1 day of the procedure.
- PT/PTT – within 2 days of the procedure.
- Medical clearance within 1 week of the procedure.
- Having confirmed no evidence of EAC during 3 RFA failures and no endoscopic and histologic evidence of EAC at the time of treatment.
- Biopsy-proven RFA-recalcitrant Barrett's Esophagus with low- or high-grade dysplasia – within the past 3 months.
- Ideally, subjects should not be on aspirin or Clopidogrel therapy, but if they are, there should be no history of bleeding during endoscopic treatments.

4.10 Prior and Concomitant Therapy

Subjects will be randomized to either EndoRotor® or continued ablative therapy arms – no other treatments are allowed for study subjects. Endoscopic surveillance and biopsies every 3 months will be performed in both groups. Subjects with refractory Barrett's metaplasia after 3 failed radiofrequency ablations (RFA) are eligible for this study.

4.11 Informed Consent

Prior to the EndoRotor® procedure and enrollment in the ENDOROTOR study, written informed consent will be obtained in accordance with 21 CFR 50.20 and contain the information required by each of the eight basic elements of 21 CFR 50.25(a).

4.12 Inclusion Criteria

Candidates for this study must meet **ALL** of the following Inclusion criteria:

1. Subjects who are ≥30 and <79 years of age; inclusive of males and females.
2. Subjects with a history of confirmed Barrett's esophagus with dysplasia (low-grade or high-grade) refractory to radiofrequency ablation 3 times.
3. Residual Barrett's length is ≥1 cm and ≤6 cm.
4. Histologic persistence of intestinal metaplasia (any non-squamous epithelial lesion) following treatment and failed eradication.
5. Following 3 failed RFA procedures with no confirmed evidence of EAC and having confirmed no endoscopic and histologic evidence of EAC at the time of therapy.
6. Subject capable of giving informed consent.
7. Subject has a reasonable expectation for prolonged survival (greater than 5 years).
8. Subject can tolerate repeated endoscopic procedures.
9. Absence of strictures that preclude the passage of the endoscope.
10. Subjects with the ability to understand the requirements of the study, who have provided written informed consent, and who are willing and able to return for the required follow-up assessments through 6 months or 9 months, as indicated.

4.13 Exclusion Criteria

Subjects will not be included in the study if **ANY** of the following exclusion criteria are met:

1. Subject unable to give informed consent.
2. Subject is unwilling to return for repeated endoscopies.
3. Subject having 3 failed RFA procedures and confirmed endoscopic and histologic evidence of EAC at time of therapy.
4. Residual Barrett's longer than 6 cm.
5. Subjects with nodular Barrett's Esophagus.
6. Subjects who are on aspirin or anticoagulant therapy who cannot stop it and have had bleeding problems during previous endoscopic treatments.
7. Esophageal varices.
8. Active esophagitis.
9. Esophageal stricture preventing passage of endoscope or catheter.
10. Any previous esophageal surgery, except fundoplication without complications.
11. Medically uncorrectable hypotension or hypertension.
12. Any condition that in the opinion of the investigator would create an unsafe clinical situation that would not allow the patient to safely undergo an endoscopic procedure (lack of medical clearance).
13. Pregnant or lactating women or women of childbearing potential who do not employ a reliable method of contraception as judged by the Investigator, and/or are not willing to use reliable contraception for the duration of study participation.
14. Patient has known severe psychiatric disorder, substance abuse, or other reason for being unable to follow trial follow-up instructions.
15. Patient has a known significant concomitant illness with a life expectancy of <1 year.
16. Patient is known to be currently enrolled in another investigational trial that could interfere with the endpoint analyses of this trial.

4.14 Study Withdrawal & Lost to Follow Up

Study participation is voluntary and subjects may withdraw their consent at any time. **ALL** enrolled subjects and their status in the study will be included in the study reports.

- **Treated and Study Criteria Not Met:** Subjects who are enrolled and treated, but who are later discovered to not meet all of the study criteria, will remain in the study and complete all of the study testing and follow-up requirements. A protocol deviation will be completed for study subjects who are found to be ineligible after enrollment. These subjects may be excluded from the Per Protocol analysis depending upon the nature of the protocol deviation.

- **Patient Withdrawal:** Participation in any clinical investigation is voluntary and a patient is allowed to discontinue their participation at any time. Subjects may withdraw at their own discretion with or without reason and without any impact on their continued medical care. If a patient voluntarily withdraws from the study, no additional medical data will be collected and the patient will not continue in the study.

- Subjects who withdraw from the study will not be replaced; however, if a patient withdraws their consent **BEFORE** being treated with the study device (before insertion of the catheter into the esophagus), and/or before the 9-month follow-up, he or she will not be included in the Per Protocol

analysis.

- **Investigator Termination:** The site Investigator may terminate the patient's procedure if it is in the patient's best interest not to continue; however, the patient is not withdrawn from the study and will be included in the PP analysis.

- **Lost-to-Follow-up:** A patient who does not complete follow-up requirements and does not officially withdraw from the study is considered lost-to-follow-up. This does not apply to missed visits where the patient misses one of the follow-up contact time points, but completes the subsequent one. In order to consider a patient lost-to-follow-up, site personnel should make all reasonable efforts to locate and communicate with the patient. All attempts to contact the patient must be recorded in the study notes, including the date, time, and name of site personnel who have attempted to contact the patient.

5.0 STUDY PROCEDURES

5.1 Overview of Study Procedure and Flow of Patient Care

Refer to **Appendix 1** for a Schedule of Study Assessments.

5.1.1 Baseline Evaluation, not greater than 3 months prior to the Index Procedure

The following baseline evaluations will be assessed and recorded on all subjects who provide written informed consent:

- Demographic information and medical history including risk factors
  - PT/PTT within 2 days of the procedure
  - Pregnancy test within 1 day of the procedure
  - Cryotherapy treatments
  - Assessment against Inclusion/Exclusion criteria
- Medical clearance within 1 week of the procedure
- Biopsy-proven RFA-recalcitrant Barrett's Esophagus with low- or high-grade dysplasia – within the past 3 months.

5.1.2 Baseline Demographics and Relevant Medical History

The subject's demographic information and relevant medical history will be documented in the subject's source medical record and on the appropriate case report form (CRF). This will include the subject's:

- Age
- Gender
- Height
- Weight
- Race and Ethnicity Information
- Relevant medical history
- Physical Examination

5.2 Randomization Scheme

Randomization will be performed within 2 weeks of the procedure separately within each site using a 1:1 ratio

to EndoRotor® or continued ablative therapy, with blocking to be specified in separate randomization documentation. A total of 110 sealed envelopes, 55 of which contain a designation of "EndoRotor® resection" and the other 55 with the designation "Continued Ablative Therapy" will be produced. The investigator will have access to the envelopes and will designate one other person at each site to be in charge of distributing the envelopes during recruitment. The envelopes will be stored in a locked cabinet within a secure locked office at the site. If patients are lost to follow-up, additional envelopes will be provided to the site.

5.3 Laboratory Tests

Results from the subject's following laboratory tests will be documented in the subject's source medical record and on the appropriate CRF:

- Urine pregnancy test if female of child-bearing age within 1 day of procedure

5.4 Pain Assessment

Subjects will be asked to describe their pain level using a visual analog pain scale just before the index procedure. Subjects will be asked to describe their pain level using the same pain scale prior to discharge and will be compared to the pre-procedure assessment. Pain assessment will be repeated at each follow up visit. The assessments will be recorded on the case report forms.

5.5 Index Procedure

5.5.1 Eligibility

The Investigator will verify informed consent and confirm the subject meets all inclusion / exclusion criteria. The Investigator, or designee, will record in the subject's source medical record that informed consent was verified, and all inclusion / exclusion criteria were confirmed prior to the index study procedure.

5.5.2 Screen Failures

Enrolled subjects failing to meet inclusion / exclusion criteria at the time of index procedure will not be treated with the EndoRotor® device or the control device and; therefore, are classified as screen failures. Any baseline study data captured in the CRFs will be collected. Only subjects in whom the EndoRotor® catheter or ablative therapy catheter enters the esophagus will be followed and study data analyzed [per protocol set (PPS)].

5.5.3 Index Procedure

Once enrolled, each patient will be randomized into either the EndoRotor® mucosal resection arm or the control ablation arm. Randomization will occur within 2 weeks of the procedure. The investigators shall follow the technique described by the manufacturer's instructions as provided in the Instructions for Use.

Endoscopic treatment of the esophagus will be performed within 6 weeks of enrollment with outpatient video documentation of the residual Barrett's changes during upper endoscopy.

EndoRotor® Arm: At this point, the EndoRotor® will be set-up and used to resect the mucosa and submucosa to remove all gross visible disease. Lesions will be "lifted" using saline solution with dye such as Indigo carmine or Methylene Blue. Indelible ink (such as SPOT) will be injected into the region of the resection to identify the site after resection. If the lesion is circumferential, the endoscopist shall resect no greater than 270 degrees of the radial circumference of the esophagus to avoid stricture formation. The resection is taken down to the muscularis propria layer to ensure all of the mucosa and submucosa is removed in the area of persistence.

The EndoRotor® is set to either High Speed (1700 RPM) or low speed (1000 RPM) based on user preference and the vacuum is set to between 250 mmHg and 350 mmHg of negative pressure. The endoscopist will start the EndoRotor® motor using the left foot pedal, and will activate the cutting by depressing and holding the

right pedal down for as long as he wants to resect tissue. The procedure is repeated until the entire gross visible lesion has been removed down to the muscularis propria without entering the muscle layer. The specimen can be sent to Pathology by removing the filter in the specimen trap. A new filter is placed in the specimen trap allowing multiple lesions to be treated and analyzed histopathologically.

Continued Ablative Therapy Arm: The investigator shall exercise standard of care for continued ablative therapies namely RFA (HALO 90/60) and/or cleared cryotherapy devices. These will constitute two control devices. The investigator will choose the system in this arm. Operation of the each system will be done according to the manufacturer's instructions for use. The type of system used will be indicated on the case report forms.

5.6 Follow-Up Procedures and Therapy Transitions

Surveillance endoscopy is performed in 3 months where there is visual inspection of the treated areas. Biopsies are taken from the areas treated with the respective device are sent to pathology to evaluate for the presence of intestinal metaplasia (Barrett's). If the samples are read as negative by Pathology (no Barrett's seen), the patient then undergoes another endoscopy in 3 months. If the results again are negative, the patient is declared to have a complete response to the treatment (EndoRotor® or ablative therapy).

If there is intestinal metaplasia (Barrett's) confirmed by the biopsy, the patient undergoes a second treatment with either the EndoRotor® or ablative therapy as described in Section 5.7. Two consecutive negative results at 3 month intervals between biopsies is required to consider these subjects complete responders.

If there is intestinal metaplasia (Barrett's) seen either at 90 days or at 180 days after either (EndoRotor® or cryotherapy / ablative therapy) second treatment, the patient is considered to have failed and will exit the study.

To evaluate the secondary endpoint of this study, "Percent reduction of the area with Barrett's esophagus that was resected or ablated during the initial treatment session through the final follow-up visits", percent reduction of the area with Barrett's esophagus will be determined by a decrease in overall length. Using the Prague criteria, both the circumference and maximal length of the Barrett's segment will be estimated. A percentage reduction in the length will be calculated by length measured at the follow up endoscopy divided by the total prior length.

Adverse events, as defined in Section 10.4, will be recorded from the index procedure (Day 0) through study completion and/or exit/withdrawal.

5.6.1 Procedural Details

The EndoRotor® will be set-up and used to resect the mucosa and submucosa to remove all gross visible disease. If the lesion is circumferential, the endoscopist shall resect no greater than 270 degrees of the radial circumference of the esophagus to avoid stricture formation. The resection is taken down to the muscularis propria layer to ensure all of the mucosa and submucosa is removed in the area of persistence.

Details of the subject's index procedure will be documented in the subject's source medical record and on the appropriate CRF, including:

- Date of Procedure
- Preoperative Diagnosis
- Method and Type of Sedation
- Concomitant Procedures Performed
- Verification of resection results

- Time of endoscope insertion and beginning of EndoRotor use
- Time the Procedure was Completed (end of EndoRotor use and time endoscope removed)
- Estimated Blood Loss
- Postoperative Diagnosis
- Lot and Serial Number of the EndoRotor® console and catheter
- Any Adverse Events

5.6.2 Post-Procedure Evaluations

Subjects will be discharged from the hospital upon satisfactory completion of all post-procedure recovery requirements as defined by the investigational site's standard protocol.

Post-procedure pain and dysphagia will be recorded for all subjects after each intervention.

Adverse events will be recorded in the subject's source medical record and on the appropriate CRF as they are observed.

5.7 Subject Follow-Up

If at any point during post-procedure subject follow-up, a subject's clinical presentation jeopardizes the safety or welfare of the subject, the Investigator should act in the best interests of the subject, utilizing any and all means judged medically necessary.

All endoscopic assessments will be saved in digital format. All files will be de-identified to maintain subject's confidentiality and submitted to the Sponsor along with the CRFs for data analysis.

5.7.1 Possible Follow-Up Scenarios

There are several scenarios with respect to each individual subject's timeline, regardless of which arm they are in.

5.7.1.1 Scenario 1 – Complete Response with negative biopsies on 2 consecutive surveillance endoscopies. The subject undergoes a treatment and returns in 3 months for surveillance. The biopsies are negative. The subject returns for his/her second surveillance endoscopy in 3 months and is found to have negative biopsies again. The subject is considered a complete responder and is taken out of the study. Time in the study is 6 months after the initial treatment, or about 7 months after recruitment.

5.7.1.2 Scenario 2 – Failure to clear disease with a positive biopsy after a second treatment with the EndoRotor® or continued ablative therapy. The subject undergoes a treatment and returns in 3 months for surveillance. The biopsies are positive. The treatment is performed again depending on which arm he/she is in (EndoRotor® or continued ablative therapy). The subject returns for his/her surveillance endoscopy in 3 months after the repeat treatment and is found to have positive biopsies again. The subject is considered a failure to respond and is taken out of the study. Time in the study is 6 months after the initial treatment, or about 7 months after recruitment.

5.7.1.3 Scenario 3 – Complete Response despite one positive biopsy. The subject undergoes a treatment and returns in 3 months for surveillance. The biopsies are positive. The treatment is performed again depending on which arm he/she is in (EndoRotor® or continued ablative therapy). The subject returns for his/her surveillance endoscopy in 3 months after the repeat treatment and is found to have negative biopsies. The subject returns for his/her surveillance endoscopy in 3 months and is found to again have negative biopsies and is considered a complete responder

and is taken out of the study. Time in the study is 9 months after the initial treatment, or about 10 months after recruitment.

5.7.1.4 Scenario 4 – Failure to clear disease despite one negative biopsy. The subject undergoes a treatment and returns in 3 months for surveillance. The biopsies are negative. The subject returns for his/her second surveillance endoscopy in 3 months and is found to have positive biopsies. The treatment is performed again depending on which arm he/she is in (EndoRotor® or continued ablative therapy). The subject returns for his/her surveillance endoscopy in 3 months after the repeat treatment and is found to have negative biopsies. The subject returns for his/her surveillance endoscopy in 3 months and is found to have positive biopsies and is called a failure to respond and is taken out of the study. Time in the study is 12 months after the initial treatment, or about 13 months after recruitment.

5.7.2 Follow-up Visit 3-Months (± 14 days)

All subjects will return to the outpatient clinic for the 3-month visit. In the EndoRotor® arm, the EndoRotor® will be set-up and used to resect the mucosa and submucosa to remove all gross visible lesions. If the lesion is circumferential, no greater than 270 degrees of the radial circumference of the esophagus to avoid stricture formation should be treated during the procedure. The resection is taken down to the muscularis propria layer. Results of the following study procedures will be recorded in the subject's source medical record and on the appropriate CRF:

- Surveillance endoscopy
- Resection or ablation with the EndoRotor or cryotherapy / ablative therapy device, respectively, if lesions are present
- Adverse events
- Biopsy
  - Record biopsy results
  - Record the reduction in the number of activated fibroblasts in the submucosa of the healed resection areas

5.7.3 Follow-up Visit 6-Months (± 14 days)

The subject will return to the outpatient clinic for the 6-month visit. In the EndoRotor® arm, the EndoRotor® will be set-up and used to resect the mucosa and submucosa to remove all gross visible lesions. If the lesion is circumferential, the endoscopist shall resect no greater than 270 degrees of the radial circumference of the esophagus to avoid stricture formation. The resection is taken down to the muscularis propria layer. Results of the following study procedures will be recorded in the subject's source medical record and on the appropriate CRF:

- Surveillance endoscopy
- Resection or ablation with the EndoRotor or continued ablative therapy device, respectively, if lesions are present
- Adverse events
- Biopsy
  - Record biopsy results
  - Record the reduction in the number of activated fibroblasts in the submucosa of the healed resection areas

Should the endoscopy demonstrate complete absence of Barrett's esophagus at this visit (and they were negative at the 3-month surveillance), the subject will not need to return for the 9-month visit and will exit the study.

5.7.4 Follow-up Visit 9 Months (± 14 days)

The exam at 9 months is only required if there was evidence of Barrett's esophagus at one of the preceding two exams.

The subject will return to the outpatient clinic. In the EndoRotor® arm, the EndoRotor® will be set-up and used to resect the mucosa and submucosa to remove all gross visible lesions. If the lesion is circumferential, the endoscopist shall resect no greater than 270 degrees of the radial circumference of the esophagus to avoid stricture formation. The resection is taken down to the muscularis propria layer. Results of the following study procedures will be recorded in the subject's source medical record and on the appropriate CRF:

- Surveillance endoscopy
- Resection or ablation with the EndoRotor or continued ablative therapy device, respectively, if lesions are present
- Adverse events
- Biopsy
  - Record biopsy results
  - Record the reduction in the number of activated fibroblasts in the submucosa of the healed resection areas

All subjects will exit from the study after this visit; however, all subjects should be followed according to the Investigator's clinical standard practice guidelines for safety.

5.7.5 Unscheduled Visits

The subject may return to the outpatient clinic or phone the physician for any reason in their judgment, or in the judgment and upon request of the Investigator. Should such visit(s) occur, the Investigator will record all unscheduled visit findings, phone calls, endoscopy and laboratory results in the subject's source medical record and on the appropriate CRF.

5.8 Laboratory Testing Procedures

5.8.1 Specimen Preparation (EndoRotor® Arm Only)

The EndoRotor® specimen trap has a 1 micron filter that can be replaced once the lesion is fully removed. The trap is opened and the filter is removed and placed into a small jar with 10% formalin and then is sent to Pathology for histologic evaluation. Samples will be labeled in a blinded manner before being sent to pathology; however, it should be noted that ablative therapies do not allow for retrieval of pathology. Therefore, only the EndoRotor will include pathology from actual procedure.

Surveillance endoscopy biopsies will be obtained using standard endo-forceps and will be sent to Pathology in small jars of 10% formalin. Using the Prague Criteria to assess lesions that were previously treated the lesion can be biopsied using the Seattle Protocol which requires 4 quadrant biopsies per 1cm of length in the involved segment according to the standard of care for follow-up endoscopy. In the case of patients receiving EndoRotor treatments the patients are only receiving treatment on up to 270 degrees of surface area to avoid risk of stricture. Therefore, only positive biopsies in the EndoRotor® treated segment will be considered for further ablation. If biopsies in the EndoRotor treated section are negative they will continue with the follow-up endoscopy of the protocol until a second negative endoscopy according to the follow-up protocol. In a sub-set of the first 5 subjects (n=5), abnormal submucosal glands and fibroblasts will be harvested to determine the activity of cancer-associated fibroblasts in the submucosa before and after use of the EndoRotor® device. Dysplasia associated fibroblasts will be identified by their association with irregular shaped glands by Volume Laser Endomicroscopy. The areas will be marked using the laser marking device available on the VLE device.

After marking the areas with the system using two marks approximately a centimeter apart, the targeted area will be biopsied twice using a "keyhole" technique. This will ensure acquisition of the appropriate submucosal tissue.

5.8.2 Specimen Handling and Storage

Patient biopsy samples will be labeled per standard operating procedures of the site. The specimens are to be stored in Pathology and are subject to the rules and handling/storage/release of information regulations within the Department of Pathology.

Biopsy specimens will be processed and sections stained for the presence of dysplasia associated fibroblasts. These will be characterized by immunohistochemistry being positive for α-SMA and vimentin while negative for desmin and pan-cytokeratin.

5.8.3 Specimen Analysis

The resident pathologist shall be responsible for the review and interpretation of specimens collected.

6.0 Risks / Benefits Assessment

6.1 Risks to the Patient

The EndoRotor procedure poses no new risks to the patient than the commonly used mucosal resection techniques. As with all endoscopic resection and ablation devices, the most common risks are perforation and bleeding requiring intervention. Bleeding requiring intra-procedure intervention is not considered a serious adverse event and while it can occur it can be managed intra procedurally. Subjects may experience discomfort and pain post-procedure and after one to two days of the procedure. Other commonly known risks to a resection or ablation device include the following:

- Delayed bleeding occurring after the patient has been discharged requiring hospitalization and intervention
- Undiagnosed perforation resulting in free air in the mediastinum post-procedure

These are all common to established mucosal resection / ablation techniques and endoscopists are well practiced in handling these events. There are no additional risks that are particular to the EndoRotor® mechanical resection devices.

6.2 Mitigation Measures to Minimize Risk

All efforts will be made to minimize these potential risks by:

- Selection of qualified investigators and a qualified investigational center;
- Training the Investigator(s) on proper technique for EndoRotor® technique;
- Observation of procedures by the Interscope, Inc. and/or clinical personnel;
- Defining clear inclusion/exclusion criteria that ensure only appropriate subjects are enrolled and treated;
- Ensuring that the treatment and follow-up of subjects is consistent with current medical practice;
- Careful monitoring of adverse events, serious adverse events and device malfunctions by an Independent 3-Member Data Monitoring Committee and Interscope, Inc.;
- Adjudication of adverse events by an Independent 3-Member Data Monitoring Committee;
- Scheduled monitoring visits to the investigational site; and

- Regular communication with Investigator(s) and staff.

6.3 Potential Benefits to the Patient

The potential benefits of the EndoRotor® device are as follows:

- May be more comfortable (less pain) for the patient
- Complete removal of refractory BE lesions requiring no further treatments

7.0 STATISTICAL METHODS

7.1 General Principles

By-subject listings will be created for each CRF module. Summary tables for continuous variables will contain the following statistics: N, mean, median, standard deviation, minimum, maximum, and 95% confidence interval (CI) as appropriate. Summary tables for categorical variables will include N, percentage, and 95% CIs on the percentage. CIs for proportions will be calculated using the Clopper- Pearson exact method. Graphical techniques will be used when such methods are appropriate and informative. Tables will separate data by treatment arm.

Transformations of the data may be explored if warranted by the distribution of the data. Analyses resulting from transformations applied after the data are unmasked will be considered to be exploratory.

Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance. All analyses will be performed using SAS® (Version 9.4) and graphs using R, version 3.3.1 or later, or using SAS®.

7.2 Analysis Populations

The safety analysis population is defined as all subjects who are treated with either EndoRotor® or continued ablative therapy. Subjects will be analyzed as treated.

The primary effectiveness analysis population is intent to treat (ITT), defined as all subjects who are randomized. Subjects will be analyzed as randomized. Missing primary and secondary endpoint data will be imputed.

A supportive effectiveness analysis population is Per Protocol (PP). This population is a subset of ITT and requires that subjects be treated with either EndoRotor® or continued ablative therapy, meet all inclusion/exclusion criteria, and are evaluated for effectiveness at no fewer than two post-treatment visits 3 months apart. Subjects will be analyzed as treated. Missing data will not be imputed.

7.3 Sample Size

Assuming a response rate for Barrett's esophagus with EndoRotor® ablative therapy of 80%, and for cryoablation of 50%, the study will have over 95% power to demonstrate non-inferiority (NI), given a NI delta of 10%, of EndoRotor® to cryoablation and will have 91.6% power to demonstrate superiority of EndoRotor® over continued ablative therapy using a sample size of 110 evaluable subjects, 55 in each treatment group.

7.4 Statistical Analysis

The Primary effectiveness endpoint will be compared across treatment arms using a logistic regression, where the predictor variable is treatment arm with EndoRotor® coded 1 vs 0 for cryotherapy or ablative therapy (i.e., control). Covariates included in the model will be: subject's age, dysplasia (low-grade or high-grade), length of Barrett's lesion in cm, and duration of disease (months). The lower boundary of the predicted proportion

difference will be used to compare the two arms for the non-inferiority test and for the subsequent superiority test. In the event that missing data are present in the ITT analysis population, then multiple imputation will be performed with SAS procedures MIIMPUTE and MIANALYZE, as described in section 7.5.

The secondary endpoint, percentage reduction, will be compared using a Wilcoxon rank-sum test. In the event of missing data, The ITT analysis will be performed with data imputed by multiple imputation.

In the event of missing data, sensitivity analyses will be performed for the ITT analysis population using best case and worst case analyses as described below. Discrepant findings will be followed by tipping point analyses.

7.5 Missing Data

1. If there are missing primary endpoint data, then ten imputations of missing binary primary endpoint will be produced using SAS PROC MI using the Markov chain Monte Carlo algorithm. The seed used to begin random number generation will be 20170623. The following variables will be used as predictors: site, subject's age, dysplasia (low-grade or high-grade), length of Barrett's lesion in cm, and duration of disease (months). Analysis with SAS PROC MIANALYZE will follow.

2. For the secondary endpoint, percentage reduction, ten imputations will be produced for the randomized cohort using SAS PROC MI. The seed used to begin random number generation will be 20170623. The Markov chain Monte Carlo method will be used to compute full imputations using the following variables: site, subject's age, dysplasia (low-grade or high-grade), length of Barrett's lesion in cm, and duration of disease (months). Analysis with SAS PROC MIANALYZE will follow.

The following secondary analyses will be performed to assess the sensitivity of the results to missing data for the primary effectiveness endpoint.

- The best-case scenario will assume success for all missing data treated with EndoRotor and failure for all missing data treated with control.
- The worst-case scenario will assume failure for all missing data treated with EndoRotor and success for all missing data treated with control.
- If the best and worst case analyses lead to different statistical conclusions, then a tipping point analysis will report the proportion of successes or failures for each arm at point the statistical conclusion would change.

A similar approach will be used for the continuous percentage secondary endpoint. Best case will assume 100% removal for EndoRotor® and 0% for control; worst case will assume 0% removal for EndoRotor® and 100% for control; If the results differ using the two imputation rules, then the imputed values will be incremented on 1% values until the point where the conclusion changes is identified.

7.6 Effectiveness Hypotheses

Primary Endpoint Hypothesis 1 (non-inferiority): It is hypothesized that EndoRotor® will not have fewer subjects with complete removal than those treated with control.

$$\text{Null Hypothesis:} \quad \pi E - \delta \leq \pi C$$
$$\text{Alternate Hypothesis:} \quad \pi E - \delta > \pi C$$

Where πE=Proportion with successful treatment in EndoRotor® arm; πC= proportion with successful treatment in the control arm and δ is a non-inferiority margin of 10% (which is subtracted from πE).

Primary Endpoint Hypothesis 2 (superiority): The proportion of subjects with successful eradication areas of Barrett's metaplasia will be greater for those treated with EndoRotor® than for those treated with control.

Null Hypothesis: $\pi E \leq \pi C$
Alternate Hypothesis: $\pi E > \pi C$

Where πE=Proportion with successful treatment in EndoRotor® arm; πC= proportion with successful treatment in the control arm.

Secondary Endpoint Hypothesis: The percentage tissue removal of Barrett's metaplasia will be greater for those treated with EndoRotor® than for those treated with control.

Null Hypothesis: $\mu E \leq \mu C$
Alternate Hypothesis: $\mu E > \mu C$

Where μE=mean % tissue removal for EndoRotor® arm; μC= mean % tissue removal for control arm.

7.7 Safety Hypotheses

Safety is assessed by the rate of anticipated complications due to treatment. The primary compilations expected are strictures, bleeding, and esophageal perforation). It is hypothesized that the complication rate in the EndoRotor arm will be no greater than in the control arm.

Null Hypothesis: Erate > Crate

Alternate Hypothesis: Erate < Crate

Where:

Erate = Rate of Bleeding, Perforation and Stricture for EndoRotor

Crate = Rate of Bleeding, Perforation and Stricture for Control

Testing will be completed using Fisher's Exact test with two-tailed α = 0.05

Further, subsets of complications assessed to be serious (e.g., serious adverse events) will be compared, as appropriate.

7.8 Statistical Analysis of Primary and Secondary Effectiveness Endpoints

In testing for non-inferiority of the primary effectiveness, a two-tailed 95% confidence interval (CI) for the difference in two rates will be used to examine the location of the lower boundary of the CI relative to the 10% NI delta. An NI delta of 10% is judged to be clinically acceptable for this indication. Further, given an expected 30% advantage of the test device over the active control (80% vs 50%), by setting the non-inferiority margin at 10%, we are retaining 67% of the active treatment advantage as opposed to a using a

more standard value of 50% (Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) November 2016 Clinical/Medical).

In testing for superiority of the primary effectiveness endpoint, the same logistic regression model, used to test for NI will be evaluated. Alpha of 0.05 will be used to test for significance.

The secondary effectiveness endpoint will be tested with a Wilcoxon rank-sum test. An alpha of 0.05 will be used to test for significance.

7.8.1 Site Effect

The consistency of the success rate over investigational sites will be assessed. Success proportions by site will be summarized. A Fisher's exact test will be used to examine the significance of a difference in the primary effectiveness endpoint using an alpha of 0.15.

7.8.2 Interim Analysis

No interim analysis of effectiveness endpoints will be performed.

7.8.3 Multiplicity

In the event that the primary effectiveness test of non-inferiority fails to reach significance, further endpoint testing will cease. If the test of non-inferiority is successful, then testing for superiority will proceed. If superiority is demonstrated for the primary effectiveness endpoint, then the secondary endpoint will be tested.

7.8.4 Additional Summaries

Subject baseline and demographic characteristics, including medical history, and operative characteristics and outcomes will be summarized for each treatment arm. Subject disposition and protocol deviations will be summarized by count and percentage. All summarized data will be supported by subject line listings.

8.0 INVESTIGATOR RESPONSIBILITIES

The Site Investigators are responsible for signing the Investigator agreement prior to the commencement of the study and for ensuring that this trial is conducted according to this clinical protocol, Good Clinical Practice (GCP) Guidelines, the Declaration of Helsinki, US FDA requirements and any other local, or IRB requirements that apply to Clinical Investigations at their center.

It is the also the Investigator's responsibility to ensure that all sub-investigators and staff assisting with this study have the appropriate qualifications and that they complete training on the investigational devices and study procedures and that patient confidentiality is respected.

8.1 Institutional Review Board (IRB) Approval

The Investigator at each site is responsible for securing IRB approval for this study protocol and the Informed Consent documents prior to any patient enrollment. The local IRB for each specific institution or for multiple institutions must review and approve this study protocol and the specific Informed Consent forms to be used at that site **prior** to enrollment of the first patient. The Sponsor **must** also review and approve the final Informed Consent documents prior to their use. The Sponsor and/or their designated CRO must receive a copy of any IRB correspondence, as well as the final approval letter and the final approved Informed Consent from each IRB. Investigators are also responsible for submitting and obtaining a continuing review (at intervals

not greater than once a year) of the study by their IRB.

The Investigator or clinical site staff will not make amendments to this protocol or the Informed Consent forms without **PRIOR** written approval from the Sponsor. All approved amendments must then be submitted to the local IRB and the FDA, as appropriate for approval.

8.1.1 Withdrawal of Approval

If the Investigator's IRB withdraws their approval to conduct this study for any reason, the Investigator **must** notify the Sponsor and their designated CRO as soon as possible, but in no event later than **five working days** after the withdrawal of the approval.

8.2 Informed Consent

The Investigator is responsible for ensuring that all local, national, GCP, Declaration of Helsinki, and US FDA guidelines and regulations are met when completing the informed consent process. Written, informed consent is to be obtained whenever possible for each patient **prior** to treatment. Additional details regarding the informed consent process are also available in the Section 4.8 Screening and Enrollment of this protocol.

8.3 Clinical Data Collection

Two-ply, paper Case Report Forms (CRFs) will be used to collect complete and accurate records of the clinical data from this study according to the Good Clinical Practices (GCP) requirements. The Investigator and/or study staff under his/her direction is responsible for accurately recording the clinical data for this study and entering the data into the CRF and upload to the Sponsor's secure web server in a timely manner. The required form / report and timeframes are provided in **Table 1** below:

Table 1. Form/Report and Required Submission Timeframe

Form/Report	Required Submission Timeframe
Enrollment/Treatment Notification	Enter onto CRF and upload to Sponsor's secure web server **within 48 hours.**
Baseline and Treatment CRFs	Enter onto CRF and upload to Sponsor's secure web server **within 7 days** of the index procedure.
Discharge Data	Enter onto CRF and upload to Sponsor's secure web server **within 7 days of discharge.**
Follow-up Forms	Enter onto CRF and upload to Sponsor's secure web server **within 7 days** of follow-up visit.
Serious Adverse Events	Notify Sponsor via email **within 24 hours** of knowledge. Enter onto CRF and upload to Sponsor's secure web server within **48 hours** of knowledge.
Adverse Events	Enter onto CRF and upload to Sponsor's secure web server **within 7 days** of knowledge.
Device malfunction / Failure	Notify Sponsor via email **within 48 hours** of knowledge. Enter onto CRF and upload to Sponsor's secure web server **within 48 hours** of knowledge.

Deviations from the CIP	Enter onto CRF and upload to Sponsor's secure web server **within 7 days** of knowledge.

8.4 Device Accountability

The Sponsor will ship investigational devices only to the designated Investigators participating in this study following internal requirements, FDA IDE Conditional Approval and IRB approval. All Investigators will be responsible for providing a secure storage location for the investigational devices, supervising investigational device use, and the disposal and/or return of the investigational devices as instructed by the Sponsor. In addition, all Investigators will maintain records to document the receipt, use and disposition of all investigational devices received by their site. The Sponsor, designated monitor and/or CRO will also maintain records of all shipments and disposition of the investigational devices. The Sponsor and/or their authorized CRO will routinely inspect the clinical site inventory records for device accountability at the clinical sites participating in this trial.

8.5 Clinical Site Records

Records to be maintained by the Investigator and research staff include:

- Clinical trial investigational plan and all amendments
- Signed clinical trial agreement
- Investigator agreements
- IRB approval letter, including informed consent documents
- IRB membership list
- Correspondence relating to the trial
- CVs for all investigators and key personnel
- Clinical monitor sign-in log
- Patient screening / enrollment log
- Lab certification and lab test normal ranges
- Reports (includes annual reports, final reports from investigator and sponsor)

The following records must be maintained for each patient enrolled in the trial:

- Signed Patient Informed Consent Form
- All completed CRFs
- Supporting documentation of any complications and Serious Adverse Events

Interscope recommends that the investigator retain copies of procedure reports, procedure notes and the results of any interventional procedures that occur after the endoscopy procedures.

8.6 Investigator Reports

8.6.1 Serious Adverse Events (SAEs) & Unanticipated Adverse Events (UAEs)

The Investigators will report by telephone, email or fax any SAEs or UAEs as soon as possible, (within 24 hours) of the Investigator becoming aware of the event, to the Sponsor and the CRO. Additionally, SAEs and UAEs should be reported to the IRB and/or FDA (if applicable) per the clinical site guidelines. The Serious Adverse Event form is to be uploaded to the Sponsor's secure web server within 48 hours of the event. The contact information for reporting SAEs and UAEs is provided in the Study Contact section of this protocol.

8.6.2 Device Malfunctions

The Investigators will report any Device Malfunction that occurs to Interscope as soon as possible, or within 48 hours of the Investigator becoming aware of the event. The report may be made by telephone, email or fax. Additionally, when a device malfunction occurs, or is suspected to occur during treatment, the Investigator must keep the device in a safe storage facility until an investigation can be completed and/or the designated monitor or a Sponsor representative directs the Investigator or study staff to return the device to Interscope for investigation.

8.6.3 Deviations from the Investigational Plan

The Investigator must notify Interscope and/or the CRO of any deviation from the Investigational Plan. The Investigator should also notify the IRB and/or FDA as required per their local requirements. This notice must occur as soon as possible, but in no case longer than five working days after the Investigator becomes aware of a serious deviation. Serious deviations include those that involve the informed consent process, the inclusion/exclusion criteria of the study or any deviation that involves or leads to a serious adverse event in a study participant.

8.7 Clinical Site Reports

Investigators are required to prepare and submit to Interscope complete, accurate and timely reports on this investigation when necessary according to **Table 2** below:

Table 2. Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by Investigator for	Time of Notification
Enrollment/Treatment Notification	Interscope	Within 48 hours. Automatic email notification is sent to Interscope.
Serious adverse events	Interscope, IRB	Within 24 hours of knowledge of event
Unanticipated complications	Interscope, IRB	If serious or life threatening within 24 hours of knowledge of event
Patient withdrawal	Interscope	Within 10 working days
Withdrawal of IRB approval	Interscope	Within 5 working days
Annual progress report	Interscope, IRB	Submitted annually
Protocol Deviations	Interscope, IRB	Within 5 working days
Informed consent not obtained from patient	Interscope, IRB	Within 5 working days

Final report	Interscope, IRB	Within 3 months
Other information upon the request of the IRB, FDA, or Interscope	As appropriate	As requested

8.8 Investigator's Final Report

Upon completion or termination of the Interscope Study the principal investigator must submit a final written report to Interscope and the IRB as required by the IDE regulations. The report must be submitted within 3 months of completion or termination of the trial. The investigator's final report will include:

- Introduction. A brief description of the rationale and objectives of the trial.
- Methods. A description of the methods employed and any deviations from the investigational plan.
- Trial Population. A statement of the number of subjects evaluated; of the number of dropouts and reasons for them; and description of the initial nature and severity of medical conditions for which the subjects were evaluated.
- Results and Discussions. A clinical assessment of the effect of the investigational treatment on the medical condition of the subjects and a description of complications reported with an indication of their relationship to the investigational treatment.
- Conclusion. A summary statement of the principal investigator's opinion of the effectiveness of the investigational treatment in the subjects enrolled at his/her investigational site.

8.9 Deviations from Protocol

The investigator will not deviate from the protocol without the prior written approval of Interscope except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required; however, Interscope's CRO must be notified within 5 days of the incident.

8.10 Site Record Retention Policy

Records and reports will remain on file for a minimum of two (2) years after the latter of either the completion/termination of the investigational trial or the date the investigational device receives FDA clearance. They may be discarded upon notification by Interscope. To avoid error, the principal investigator should contact Interscope before the destruction of any records and reports pertaining to the trial to ensure they no longer need to be retained.

In addition, Interscope should be contacted if the principal investigator plans to leave the investigational site so that arrangements can be made for transfer of records and the remaining follow-up (if any) in the study.

8.11 Investigator Access to the Data and Publication Policies

At the conclusion of the trial, a multicenter publication/presentation reporting the primary results will be prepared and presented at a major medical meeting. A multicenter publication will also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience within the trial is strongly discouraged until the multicenter results have been prepared, presented and submitted for publication (normally 1 year following the completion of the study). The analysis of other pre-specified

and non-pre-specified endpoints will be performed by Interscope. For purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multicenter data will require the approval of the Interscope. The ENDOROTOR study will be registered with Clinicaltrials.gov per applicable requirements.

9.0 SPONSOR RESPONSIBILITIES

9.1 Role of Interscope

As the study Sponsor, Interscope, Inc. is responsible for the overall conduct and quality of the study, including the assurance that the study complies with the appropriate standards and regulations that apply to medical device clinical investigations. Interscope will also ensure adherence to the Sponsor general duties as outlined by GCP standards and the US FDA standards. Additionally, the Interscope study management will ensure that qualified monitors are monitoring the study according to the protocol, GCP standards and study regulations, and that the Informed Consent process is followed per each site's local and US FDA requirements.

9.2 General Duties (21 CFR 812. 40)

Interscope general duties, either directly or as delegated to its CRO, consist of submitting the IDE application to FDA and obtaining FDA approval for the IDE prior to shipping devices, selecting qualified investigators and clinical sites, ensuring that each site has obtained IRB approval prior to shipping devices to that site, ensuring proper clinical site monitoring and GCP compliance, and ensuring that informed consent is obtained for each enrolled patient.

Interscope will also ensure adherence to the FDA regulations and the Sponsor general duties (21 CFR 812.40), selection of investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications [21 CFR 812.35 (a) and (b)], maintaining records [21 CFR 812.140 (b)], and submitting reports [21 CFR 812.150 (b)].

Interscope will collect quality data that satisfies federal regulations including serious unanticipated adverse events and deviations from the protocol. Interscope will prepare written progress reports and a final study report at the completion of the study.

9.3 Selection of Clinical Sites & Investigators

Interscope will select qualified clinical sites and Investigators who are experienced with endoscopic resection and ablation devices. The Investigator must work with a qualified IRB to oversee the rights, safety and welfare of the study participants. The clinical site must also have an adequate patient population and the appropriate staffing and equipment to meet the requirements of the study protocol and the expected enrollment timeframes. All sites will be pre-qualified by the Sponsor or its CRO. Financial disclosures will be collected from all investigators during the site qualification process.

Interscope will ship devices only to participating investigators, obtain a signed Investigator's Agreement and provide the investigators with the information necessary to conduct the study.

9.4 Investigator & Staff Training

Training of the Investigators and clinical study staff is the responsibility of the Sponsor, Chief Medical Officer, designated monitors and/or the CRO. Training may be conducted during an Investigator meeting, a site initiation visit, or appropriate training venues. Investigators and study staff will undergo training on the study devices and study protocol prior to participating in the study. Training may encompass didactic information regarding the study devices as well as hands-on practice. Procedural technique and experience with the Interscope device will be assessed by the Trainer during the first case at each site. Observations during the

cases will also be discussed with the Investigator and study staff. Study and support staff at the clinical site will also be trained on the study protocol, eligibility criteria, the Instructions for Use, and proper storage of the device and supplies.

9.5 Monitoring

The Sponsor and/or the CRO will monitor the study and will select or designate clinical monitors who are qualified by training and experience, to monitor and oversee the conduct of the ENDOROTOR study. The clinical monitors will follow the Sponsor's standard operating procedure for monitoring and the Monitoring Plan to be written on a risk-based approach for this study. The Monitoring Plan will require evaluation of compliance with the protocol, GCP compliance, FDA regulations, and any specific recommendations made by the site's IRB and the signed Investigator and Study Agreements. Periodic phone contacts, site visits, and intermittent remote visits will be conducted to ensure that the protocol is being followed. The clinical monitor(s) will also verify that the Case Report Forms (CRFs) are in agreement with the source documentation and other records.

On-site and intermittent remote monitoring of all study sites will be frequent enough to ensure continued acceptability of the data by assessing compliance of the site to the Investigational Plan, adherence to the data collection procedures, and maintenance of study records. If necessary, appropriate corrective action will be taken to ensure adherence to the study protocol.

For record verification purposes, the monitor and/or authorized Sponsor representative will be provided access to hospital records, original laboratory data, and other records and data as they relate to the study and as agreed to with the Investigator prior to the initiation of the trial. The Investigator will also make available to the clinical monitor all regulatory documents, all completed CRFs, informed consent documents, source documentation and other relevant records for all enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If the Sponsor and/or their authorized representatives becomes aware that an Investigator is not complying with the study protocol, the Investigator Agreement, the Declaration of Helsinki, GCP standards, applicable privacy standards, or any condition of the study imposed by the IRB or the FDA, the Sponsor or their authorized representatives will immediately secure compliance or discontinue further shipments of the study devices. An inability to secure compliance and/or to complete an investigation into the factors that are inhibiting compliance may result in the Investigators termination from the study by the Sponsor.

Study close-out visits will be conducted after the final follow-up visit is completed at each site. Following the resolution of any outstanding data discrepancies and adverse events, the remaining investigational study devices will be the collected and returned to the Sponsor. A final study report will be generated and submitted to the Investigator and the appropriate study oversight authorities. Study document retention requirements will be reviewed with each site during the close-out visit.

9.6 On-Site Audits

In accordance with GCP and US FDA requirements, a Sponsor or CRO representative may request access to all study records, including source documents, for inspection and duplication. In the event that an Investigator is contacted by a regulatory agency or local IRB in relation to this study, the Investigator will notify the Sponsor or designated monitor/CRO as soon as possible.

The Investigator and/or designees must be available to respond to reasonable requests by authorized Sponsor, CRO and regulatory agency representatives during the monitoring and inspection process. The Investigator must provide the Sponsor and CRO with copies of all correspondence that may affect the review of the current study (i.e. Inspection Observations) or their qualification as an Investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits.

9.7 Records & Record Retention

The Sponsor and/or designated monitor/CRO will maintain copies of correspondence, Investigator Agreements, clinical data, device shipments, clinical events (AEs, SAEs, and UAEs), adverse device effects and other records related to the clinical trial and supporting documentation, and other records and reports related to this clinical study.

The Sponsor, core Laboratories and clinical sites will maintain the study records until 2 years after the final study report is completed, or longer if required by local or national regulatory agencies. The Sponsor and/or CRO will notify each site regarding the regulatory requirements for record retention during the study close-out visit.

9.8 Sponsor Reports

Interscope, Inc. will submit the required FDA reports identified in 21 CFR 812.150 (B). This includes unanticipated adverse device effects, withdrawal of IRB or FDA approval, current Investigator list (every 6 months), annual progress reports, recall information, final reports and protocol violations.

9.8.1 Study Data Reports

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

Upon receipt of the final study data and the final reports from each center, the Sponsor will complete a final study report. Copies of the final report will be provided to each Investigator.

9.9 Supplemental Applications

As appropriate, the Sponsor will submit changes to the study protocol to the FDA and to the Investigators to obtain IRB re-approval.

9.10 Coverage of Patient Expenses

The treated subjects will not be compensated for their time during the trial. The Sponsor may provide reimbursement for modest out-of-pocket patient costs associated with travel, parking, or other expenses associated strictly with completing the protocol requirements of this study that would not normally be covered under routine medical coverage for the patient's underlying medical condition if such reimbursement is approved in writing by the local IRB prior to study enrollment.

10.0 QUALITY ASSURANCE & ETHICAL STANDARDS

The study will be conducted according to the Declaration of Helsinki, Good Clinical Practice Guidelines (GCP), US FDA regulations, and any additional IRB requirements that apply to clinical investigations of medical devices. As the study Sponsor, Interscope has the overall responsibility for the conduct of the study, including

the assurance that the study is in compliance with these guidelines, standards and requirements.

10.1 Medical Monitor

To meet the ethical responsibilities and standards for research subjects, the Medical Monitor (Sponsor's Chief Medical Officer) will review all adverse events, serious adverse events, unanticipated adverse device effects, and in conjunction with the engineering department any device performance report, failure or malfunction that could potentially impact the treatment of, or the clinical outcomes of subjects enrolled in the study. In the event that further investigation is required for any significant clinical or device performance issue that is identified in the trial the Medical Monitor or Sponsor's Regulatory Representative will initiate a corrective and preventative action (CAPA) procedure within the Interscope Quality Management System to further investigate and resolve the occurrence.

10.2 Safety Monitoring & Study Termination

The Medical Monitor will closely monitor current medical practice, device performance, and the occurrence of and rate of occurrence of adverse events, serious adverse events, and unanticipated adverse device effects to determine if there is an unreasonable risk to the study participants. If warranted, the study protocol may be amended, and/or the study may be suspended or terminated early.

An independent Data Monitoring Committee (DMC) consisting of at least three members will review serious adverse events and safety endpoint events. Adjudication of adverse events will be conducted according to a Data Monitoring Committee Charter to be approved by the Sponsor and the DMC. The Charter will include:

- Stopping rules
- Planned Safety Reviews: Safety reviews will occur at predetermined intervals
- Unplanned Safety Reviews: Any safety concerns that arise during the trial will be brought to the attention of the IPA. A full DMC meeting can be called at the discretion of the DMC Chairperson. The DMC Chairperson may also request additional data reviews when considered necessary to monitor the progress of the trial.
- DMC reports are to include:
    - Rates of recruitment, ineligibility, noncompliance, protocol violations and dropouts, overall and by study site;
    - Completeness and timeliness of data;
    - Duration of follow-up and early study discontinuation;
    - Baseline characteristics and demographics;
    - Medical History;
    - Device data;
    - Adverse Events;
    - Serious Adverse Events; and
    - Unanticipated Adverse Device Effects
    - A significant difference in safety or effectiveness between the EndoRotor and the control devices
    - Decision on continuing or stopping the study based on safety and effectiveness of the study device and the control devices

The DMC will be determined prior to the study and records of event review will be documented and maintained in the study records. The DMC will be completely independent of the Sponsor and the ENDOROTOR study. The Sponsor may terminate Investigator and site participation in the study if there is evidence of an Investigator's failure to maintain adequate clinical standards or evidence of continued serious protocol deviations.

10.3 Data Management

All required data for this clinical study will be recorded via a validated database. This database complies with GCP requirements, laws and regulations applicable to the conduct of clinical trials, ISO 14155, and 21 CFR 11 (US Code of Federal Regulations) pertaining to the use of electronic records and signatures. System training for all research coordinators and Investigators will be conducted through instructor-led training supported with an on-line training module.

Incoming data will be frequently reviewed to identify inconsistent or missing data and any adverse events. Investigators are responsible for the accurate completion and timely submission of the data collected during this trial. Any data issues are to be promptly addressed with the Investigator by the study manager, designated monitor/CRO and/or Sponsor.

Clinical procedures have been established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed and that adverse events are correctly reported and investigated. Investigators are to maintain all source documents as required by the protocol, including laboratory results, supporting medical records and signed Informed Consent forms. The source documents will be verified during regular monitoring visits to ensure that the clinical data is complete and accurate.

10.4 Adverse Events & Definitions

A complication is defined as any clinical finding that has the potential to become clinically significant in the opinion of the investigator. A complication may progress in the level of clinical significance and become classified as an adverse event. All complications shall be recorded on the CRFs.

Adverse Events (AEs) are clinical findings that result in an untoward medical event.
Please record all AEs on the CRFs. Adverse Events will be further classified as Serious Adverse Events (SAEs) if the event:

- Is life threatening or fatal;
- Results in permanent impairment of a body structure or function;
- Results in congenital anomalies/birth defects
- Requires or prolongs hospitalization; or
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Note: Hospitalization is defined as any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect. The following definitions for rating severity of adverse events will be 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.

AEs or SAEs will also be classified as to their relationship to the device, as follows:

Not Related: The event is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the investigational device, procedure or general surgery.

Possible: The event has a strong temporal relationship to the use of the investigational device, procedure or general surgery, and an alternative etiology is equally or less likely.

Probable: The event has a strong temporal relationship to the use of the investigational device, procedure or general surgery and another etiology is unlikely or significantly less likely.

Definite: An event that can only be attributed to the use of the investigational device, procedure or general surgery.

Not Assessable: The event's relationship to the use of the investigational device, procedure or general surgery cannot be assessed.

If an AE or SAE is determined to be probably or definitely related to the investigational device and has not been previously anticipated, the clinical finding would further be classified as an unanticipated adverse device effect (UADE). A UADE is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

SAEs that are determined to be probably or definitely related to the investigational device are referred to as device-related serious adverse events (DRSAEs). The protocol definitions for "device failure", "device malfunction", and "technical observation" are provided below:

Device Failure: A device has failed if it does not perform according to the Instructions for Use provided with the device and as a result, negatively impacts the treatment, when used according to this protocol. A device failure that causes or contributed to a serious adverse event would be classified as a DRSAE.

Device Malfunction: A device malfunction is an unexpected change to the device that is not contradictory to the labeling and may or may not affect the performance of the device. A device malfunction is not considered to be a DRSAE unless it causes or contributes to a serious adverse event. **Technical Observation:** Malfunction or complaint with a medical device that has the potential to, but may or may not result in, a negative clinical consequence to the patient.

> **Note:** A device failure or device malfunction is considered to be a DRSAE if it causes or contributes to a SAE.

Any Device Failure, Device Malfunction or Technical Observation must also be documented in the CRFs.

10.5 Reporting of Adverse Events

All adverse events, including SAE's and UADE's, will be monitored from the time of enrollment through the study exit. A description of the event, including the start date, resolution date, action taken, and the outcome shall be provided, along with the Investigator's assessment of the relationship between the AE and the study device and procedure.

All AE's should be followed until the event is resolved or judged to be clinically stable. The clinical site should plan to provide additional, relevant AE follow-up information to the Sponsor upon request.

All SAEs, DRSAEs, and UADE's must be reported to the Sponsor and/or CRO and the primary Investigator at the site **within 24 hours** of the Investigator becoming aware of the event. Additionally, the Investigator should notify their IRB, and local/national authorities as required, within their specified timeframes. The Sponsor and CRO will decide whether all of the local Investigators need to be informed immediately, or whether this can be postponed until the next regularly scheduled study update.

A completed SAE CRF **must** be uploaded to the Sponsor's secure web server **within 48 hours of the event**. The minimum required data to be recorded for an SAE includes: date of event, type of event, duration of event, severity, seriousness, action taken, outcome, causality and relationship to the Interscope device and procedure. In the case of a DRSAE, whenever possible, the device involved in the failure or malfunction is to be returned to Interscope for analysis.

10.6 Privacy and Confidentiality

Privacy and confidentiality of subjects will be maintained throughout the Interscope ENDOROTOR trial. A unique identification code will be assigned to each patient participating in this trial. Access to the patient's medical records will be limited to authorized personnel of the Sponsor, their designated CRO, clinical site study staff and authorized regulatory authorities as required by the EC and/or local or national agencies. Any data that may be published in abstracts or scientific journals, and/or presented at medical meetings will reference a unique patient code and will not reveal the patient's identity. The Sponsor and their representative (CRO) will make every reasonable effort to protect the confidentiality of the subjects participating in this study.

11.0 STUDY DATA REPORTING AND PROCESSING

11.1 Data Entry, Cleaning and Editing

Development of a validated database for the trial will be performed by Interscope and/or its CRO. Interscope will also be responsible for auditing the database and confirming the overall integrity of the data.

Single data entry into the database will be done by Interscope and/or its CRO. All study records and CRFs will be subjected to initial inspection during routine monitoring visits for omitted data, gross data inconsistencies, and deviations. Any deficiencies or deviations will be resolved by the site. Any discovered errors are referred to the clinical site research coordinator for correction through a Data Clarification Form.

11.2 Final Data Analyses

All exported datasets for analyses by SAS will undergo a final data cleaning procedure using SAS programmed logical routines unique to each exported dataset.

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APPENDIX 1 – SCHEDULE OF STUDY ASSESSMENTS

A schedule of study assessments is provided below.

	Baseline (≤14 days)	Index Procedure (Day 0)[3]	Discharge	3 Months (±14 days)	6 Months (±14 days)[3]	9 Months (±14 days)[4]
Confirm Eligibility	X	X				
Informed Consent	X					
Randomization	X					
Demographics	X					
Medical History	X					
Physical Examination	X					
Pregnancy Test[1]	X					
EndoRotor® or Continued Ablative Therapy Procedure		X		X	X[4]	X[5]
Surveillance Biopsies		X		X	X[4]	X[5]
Adverse Event Assessment		X	X	X	X[4]	X[5]
Analog Pain Scale[2]		X	X	X	X	X

[1] Urine pregnancy test for female of child bearing potential within 1 day of procedure.
[2] Pain assessment should be completed just prior to each endoscopic procedure and at discharge.
[3] The index procedure must be done within 6 weeks of enrollment with outpatient video documentation of the residual Barrett's changes during upper endoscopy.
[4] The exam at day 6 months is not required if there is no presence of intestinal metaplasia (Barrett's) on biopsies from the preceding exam.
[5] The exam at day 9 months is not required if there is no presence of intestinal metaplasia (Barrett's) on biopsies from the preceding exam. See Section 5.7 Subject Follow-up.

APPENDIX 2 – INVESTIGATIONAL SITE LIST

Site Number	Principal Investigator Contact Information
001	Study Principle Investigator: Kenneth Wang, M.D. The Mayo Clinic 200 1st St SW, Rochester, MN 55905 Telephone: 1-507-284-2511 Fax: Email: Wang.kenneth@mayo.edu
002	Principle Investigator: Gregory G. Ginsberg, M.D. University of Pennsylvania Perelman Center for Advanced Medicine Gastroenterology Division South Pavilion, 7th Floor 3400 Civic Center Blvd. Philadelphia, PA 19104 Telephone: 215-662-4279 Fax: 215-349-5915 Email: gregory.ginsberg@uphs.upenn.edu
003	To be determined
004	To be determined
005	To be determined

APPENDIX 3 - DEFINITIONS

Adverse Device Effect (ADE): An adverse device effect is defined as any untoward adverse event related to the use of an investigational or unintended response to a medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, installation, operation, or any malfunction of the medical device. This definition includes any event resulting from insufficiencies or inadequacies in the Instructions for Use or the deployment of the device or any event that is a result of user error.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the medical device.

Adverse Event (AE): An adverse event (AE) is 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 study device/procedure.

Anemia: Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to below 30%. Any documented anemic event requiring ≥2 units PRBCs will be considered an SAE.

Bleeding Complication at Index Procedure: Bleeding requiring intra-procedure intervention is not considered a serious adverse event and while it can occur it can be managed intra procedurally.

Death: (divided into 2 categories)

A. Cardiac death is death due to any of the following:

1. Acute myocardial infarction.
2. Cardiac perforation/pericardial tamponade.
3. Arrhythmia or conduction abnormality.
4. Stroke within 30 days of the procedure or stroke suspected of being related to the procedure.
5. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.
6. Any death for which a cardiac cause cannot be excluded.

B. Non-cardiac death is a death not due to cardiac causes (as defined immediately above).

Delayed Bleeding: Bleeding occurring after the patient has been discharged requiring hospitalization and intervention.

Bleeding that occurs post-procedure requiring intervention.

Device Failure: A device that is used in accordance with the Instructions for Use, but does not perform according to the Instructions for Use and negatively impacts the treatment.

Device Malfunction: A malfunction of a device is an unexpected change to the device that is contradictory to the Instructions for Use and may or may not affect device performance. Includes damage, stress fracture or other failure as observed at the procedure.

Endoscopy: An examination or procedure using an endoscope to examine the inside of the alimentary tract.

Infection, systemic: Systemic infection documented by positive lab culture or clinical evidence, requiring medical treatment to treat and resolve.

Perforation: Puncture of the alimentary tract.

Serious Adverse Device Effect (SADE): A serious adverse device effect is defined as an adverse device effect that results in any of the consequences characteristics of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Serious Adverse Event (SAE): A serious adverse event (SAE) is defined an adverse event that:

- led to death,
- led to a serious deterioration in the health of the subject, that either resulted in:
- a life-threatening illness or injury, or
- resulted in a permanent impairment of a body structure or a body function, or
- required in-patient hospitalization or prolongation of existing hospitalization, or
- resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, or,
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the study plan without serious deterioration in health, is not considered a serious adverse event.

Sepsis: Organ dysfunction, hypoperfusion, or hypotension in the presence of a known or suspected infection.

Unanticipated Adverse Device Effect (UADE): A UADE is an event that occurs that has not been expected to occur with the device or during the course of the study procedures and has not otherwise been identified as a possible risk in the clinical investigations.