CLINICAL INVESTIGATION PLAN

Safety and Performance of the Motorized Spiral Endoscope (PowerSpiral) in Subjects indicated for small-bowel enteroscopy: A PMCF Registry

SAfety and Performance of the **M**otor**I**zed **S**piral **En**doscope **-** The **SAMISEN** study

Sponsor:	Olympus Europa SE & Co. KG
Investigational Device:	Motorized Spiral Endoscope (PowerSpiral) INTESTINAL VIDEOSCOPE OLYMPUS PSF-1 in combination with SINGLE USE POWERSPIRAL TUBE DPST-1 used with the motor control unit POWERSPIRAL CONTROL UNIT PSCU.
CIP Reference No.:	2018-GI (OEKG) – 01
Document Version:	Final Version 02
Elaboration Date:	23. April 2019
Amendments:	01

THE STUDY WILL BE CONDUCTED IN COMPLIANCE WITH THE DECLARATION OF HELSINKI, GOOD CLINICAL PRACTICE (GCP), DIN (EN) ISO 14155:2011, AND ALL APPLICABLE NATIONAL LAWS AND REGULATIONS.

Confidential Information

This clinical investigation plan is the confidential information of Olympus Europa SE & Co. KG and is intended solely for guidance of the clinical investigation. This investigation plan may not be disclosed to parties not associated with this clinical investigation or used for any purpose without the prior written consent of Olympus Europa SE & Co. KG.

SIGNATURE PAGE

Manager Clinical Operations:

Name, Title:
Institution:
Street:
Zip code - City:
Country:

[redacted]

.....

Coordinating Clinical Investigator:

Name, Title:
Professional Position:

Institution:
Street:
Zip code – City:
Country:

[redacted]

.....

Statistician

Name, Title
Institution
Street
Zip code City
Country

DECLARATION OF PRINCIPAL INVESTIGATOR

I have read this clinical investigation plan (CIP) and agree that it contains all the information required to conduct the trial. I agree to conduct the trial as set out in this CIP. I will not enroll the first subject in the trial until I have received approval for conduct of this study from the appropriate ethics committee and until all legal requirements have been fulfilled. I agree to obtain in the manner described in the CIP a written informed consent to participate from all subjects enrolled in this study and to keep the dated and signed consent forms for 15 years.

Site number: < Enter Site number here>

Principal Investigator: < Enter name of PI here>

_____ _____

Place, Date *Signature Investigator*

CONTACT ADDRESSES AND RESPONSIBILITIES

Manager Clinical Operations	[redacted]
Coordinating Clinical Investigator	
Safety Contact	
CRO	
Statistician	

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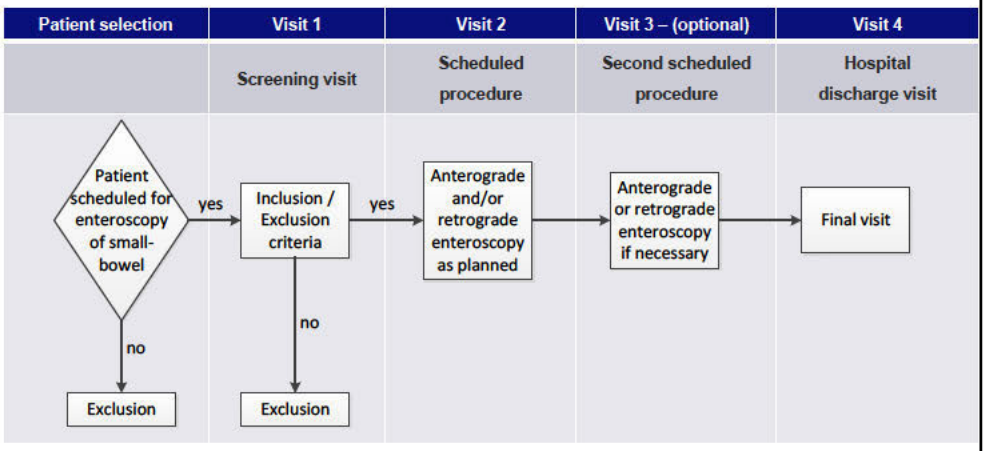
LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BAE	Balloon assisted enteroscopy
CE	Commission Européen
CIP	Clinical Investigation Plan
CCI	Coordinating Clinical Investigator
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum vitae
DBE	Double balloon enteroscopy
DIMDI	German Institute for medical documentation and information
EC	Ethics Committee
ECG	Electrocardiogram
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ISF	Investigator Site File
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SBE	Single balloon enteroscopy
SOP	Standard Operating Procedure
SDV	Source Data Verification
TMF	Trial Master File
U	Unit
WHO	World Health Organization

TRIAL SUMMARY

Title	Safety and Performance of the Motorized Spiral Endoscope (PowerSpiral) in Subjects indicated for small-bowel enteroscopy: A PMCF Registry.
Short Title or Acronym	The **SAMISEN** study (**SA**fety and Performance of the **M**otor**I**zed **S**piral **EN**doscope)
Version/ Date	CIP#: 2018-GI (OEKG) – 01 Version 2.0 (23 April 2019)
Sponsor	OLYMPUS EUROPA SE & Co. KG Amsinckstraße 63 20097 Hamburg, Germany
Purpose	Demonstrate safety and clinical performance of the Motorized Spiral Endoscope (PowerSpiral) in daily medical practice.
Objective	Prospectively collect clinical data on the application of the Motorized Spiral Endoscope (PowerSpiral) in a typical clinical setting within the Intended Use.
Endpoints	• **Diagnostic Yield:** Defined as the percentage of procedures that either confirmed a diagnosis from previous studies, or established a new definitive diagnosis at the anatomical location identified in previous studies or findings that could explain the clinical symptoms • **Therapeutic Yield:** Defined as the percentage of patients with any endoscopic intervention / therapy with the exception of biopsies • **Total procedure time:** (starting with oral /anal insertion until final withdrawal of the device) • **Total therapeutic intervention time** • **Total small bowel enteroscopy rate:** Defined as complete evaluation of the small bowel either with a single approach or combined anterograde and retrograde approach (if complete small bowel enteroscopy is intended anyway) • **Endoscopic success rate** • **Safety:** Incidence (% of subjects) and frequency (no. of subjects) with device or procedure related Serious Adverse Events (SAEs) and Device Deficiencies (DD) observed during/after the procedure • **User feedback** and assessment of handling characteristics of the device
Study Design	International, multicenter, open label, non-randomized, prospective, observational study.
Sample Size	260 subjects will be enrolled into this registry including an expected rate of 5% of losses-to-follow-up during study conduct. The first 5 procedures for each investigator will be performed to get used to the device. Data on these “learning curve” procedures will be captured and analyzed separately. The dataset for final analysis (e.g. procedure time, rate of SAEs etc.) will include 260 cases from procedure #6 onwards in order to account for a learning curve effect. The sponsor plans to activate 12 sites with one or two investigators at each site. Each site shall enroll up to 22 subjects (notwithstanding the learning curve cases) to allow for the same quota per site. Overall approximately 335 subjects will be enrolled (including cases for the learning curve).

Timelines	Study Start (Enrollment of First Patient) is planned for May/June2019. Enrollment period: 1 year (until May/June 2020). Study closure: Q2/2020.
Investigation-al Device(s) used	Motorized Spiral Endoscope (PowerSpiral) INTESTINAL VIDEOSCOPE OLYMPUS PSF-1 in combination with SINGLE USE POWERSPIRAL TUBE DPST-1 used with the motor control unit POWERSPIRAL CONTROL UNIT PSCU.
Study Population	Subjects with an indication for direct visualization of the small bowel which fulfil all inclusion and none of the exclusion criteria: **Inclusion criteria** 1. Signed informed consent 2. Patients with small bowel disease indicated for deep enteroscopy, including but not limited to: • Gastrointestinal bleeding • Crohn's disease • Abdominal pain or chronic diarrhea • Large polyps (>10–15mm) in the jejunum and ileum in patients with Peutz–Jeghers syndrome • Nonresponsive or refractory coeliac disease • Results and hints from other preliminary investigations, e.g. small-bowel capsule endoscopy, small-bowel imaging examinations etc. which warrant further work-up with antegrade and/or retrograde enteroscopy of the small-bowel **Exclusion criteria** In addition to be eligible for study enrollment a subject must not meet any of the exclusion criteria listed below. 1. Age under 18 years 2. Female and of child-bearing age who is currently pregnant or planning to become pregnant within the study period 3. Any contraindication to standard enteroscopy (e.g. severe coagulopathy or known coagulation disorder; bowel obstruction / stenosis, stents or other instruments implanted in the intestinal tract, suspected GI perforation, esophageal or gastric varices, eosinophilic esophagitis) as judged by the investigator after careful individual risk assessment 4. Concurrent participation in another competing clinical study

Data Collection	Each subject will undergo the following study visits: • ***Visit 1*** – screening visit, inform potential subjects about the trial, obtain informed consent from subjects to participate in the study, check inclusion / exclusion criteria, collect data on medical history and concomitant medication. • ***Visit 2*** **-** scheduled procedure: perform antegrade or retrograde or combined enteroscopy as planned. Provide feedback on the handling characteristics of the PowerSpiral enteroscope. • ***Visit 3*** – (optional) second procedure: retrograde (or antegrade) enteroscopy as necessary. • ***Visit 4*** – pre-hospital discharge visit: collect any (delayed) complication
Study Flow Chart	
Study Contacts	[redacted]

1 BACKGROUND AND RATIONALE

Small bowel enteroscopy is usually performed in order to evaluate gastrointestinal bleeding, small bowel tumors, polyps, inflammatory or other small bowel diseases. Video capsule endoscopy, single- (SBE), double-balloon (DBE) or spiral enteroscopy are the most popular non-surgical endoscopic techniques in this context. Hereof the endoscopic approach offers additional diagnostic and therapeutic options as biopsies and direct therapeutic intervention is possible compared to capsule endoscopy. These enteroscopy systems – also called overtube-assisted enteroscopy (OAE) techniques - are used to visualize the small-bowel and proceed with a therapeutic intervention, either during the same or in a subsequent session. For example, the DBE utilizes distal and proximal balloons that can be inflated and deflated to “anchor” and move the bowel, thereby assisting the operator in advancing the endoscope while gathering the bowel onto the overtube shaft.

However, the SBE and DBE procedures are time consuming and usually require 2 operators to perform this kind of examination.

1.1 Description of the Investigational Device

The Motorized Spiral Enteroscope (INTESTINAL VIDEOSCOPE OLYMPUS PSF-1 and SINGLE USE POWERSPIRAL TUBE DPST-1) in conjunction with the motor control unit (POWERSPIRAL CONTROL UNIT PSCU) now offers a new technology which combines the advantageous options of enteroscopy with a faster and less invasive approach. The intended use of this CE-certified medical device (PowerSpiral) is to examine the lumen of the small intestine to provide clear images for diagnostic and therapeutic purposes in the management and treatment of small-bowel disease.

The system is similar to other currently marketed endoscopes and incorporates a flexible insertion tube, light source, digital imaging, and channels for passing accessories for sample collection or therapeutic interventions. In contrast to the predecessor a novel user-controlled motor rotates a special spiral cuff (SINGLE USE POWERSPIRAL TUBE DPST-1) located on the endoscope’s insertion tube (POWERSPIRAL CONTROL UNIT PSCU). Rotation of this cuff, which has soft spiral-shaped “fins”, pleats the small bowel on to the endoscope’s insertion tube, thereby allowing rapid and atraumatic access into deeper regions of the small bowel. The Rotating speed is 30 rpm and the Rotation torque is controlled mechanically until torque limit is reached (until a limiting function is activated).

With this new medical device system deep enteroscopy allows complete visualization of the small bowel. The motorized PowerSpiral can be used for either antegrade or retrograde approach according to the operator’s preference or individual patient anatomy. The new device shall

contribute to easier and faster disease clarification and necessary therapeutic interventions in all areas of the small intestine.

The study investigators shall have considerable experience in deep enteroscopy. The study team will undergo special training (arranged by the Sponsor) to become comfortable with all handling characteristics of this novel device. The product and procedure training is mandatory prior to enrolling the first study subject and will be documented accordingly.

1.2 Justification for the Design of the Clinical Investigation

Deep enteroscopy is well established with Balloon assisted enteroscopy procedures, however there is a need for innovative and faster methods, less resource utilization which at the same time provide more comfort for the patients.

Currently available and published data for PowerSpiral was collected by means of Investigator Initiated Trials (Mans et al. 2018; Neuhaus et al. 2016; Beyna et al. 2018; Beyna 2018). With this Olympus sponsored Registry further data about performance and safety for this new medical device will be collected in a larger patient population. Obtained safety data will be compared to data published in respective guidelines or literature.

This study will be performed in parallel to the European market launch of this new medical device. It is a registry study with a CE marked medical device whose application within the intended use will be captured. The registry and does not impose any additional procedure or risk to the patient as we strive to document daily clinical routine. Therefor this study is observational (non-interventional) in nature.

For the same reason inclusion criteria are kept as broad as possible. In summary all patients are eligible where the physician realizes an indication for deep enteroscopy for further diagnostic or therapeutic work up. The exclusion criteria will only affect patients under the age of 18 years and pregnant women. Otherwise clinical judgement of the treating physician is the only relevant and leading reason for exclusion. Of course giving signed informed consent by all study subjects is a prerequisite for participation in this “registry”.

For this study approximately 12 European sites will be recruited that offer deep enteroscopy to their patients. This international multi-center setup will give a more representative picture and avoid a single-site bias. Furthermore enrollment will be completed earlier compared to a single center approach.

The prevailing complications of a deep enteroscopy are pancreatitis, perforation, bleeding and adverse events associated with sedation or anesthesia (Aktas et al. 2010; Akarsu et al. 2014; Akerman and Cantero 2009; Arulanandan et al. 2016; He et al. 2013; Moeschler and Mueller 2015). Generally these are independent if the procedure was performed as a diagnostic or therapeutic procedure however the complications rate is usually higher in interventional cases (Rondonotti et al. 2018).

The main objective of the SAMISEN study is to assess the performance and safety of diagnostic and therapeutic procedures with the newly designed Olympus Motorized Spiral Enteroscope (INTESTINAL VIDEOSCOPE OLYMPUS PSF-1 and SINGLE USE POWERSPIRAL TUBE DPST-1) system in combination with the motor control unit (POWERSPIRAL CONTROL UNIT PSCU). All Serious Adverse Events (SAE) observed in this study will be documented so the overall SAE rate as well as the number of individual types of complications (bleeding, pancreatitis etc.) can be calculated.

The very recent publication of Rondonotti (Rondonotti et al. 2018) for device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders represents an excellent source for comparison. Hence this study is designed as a prospective study without control group. The resulting SAE rate will be compared to the historical data from this ESGE Technical Review (Rondonotti et al. 2018).

The performance will be characterized by calculating the Diagnostic and Therapeutic Yield, Total Procedure Time, time needed for Therapeutic Intervention, Total Small Bowel Enteroscopy Rate and user feedback on device handling.

1.3 Risks and Benefits

All patients present a medical challenge which requires a deep enteroscopy for diagnostic and/or therapeutic purpose(s). Independent of the clinical study this kind of examination has certain clinical risks associated with such a procedure which must be balanced again other treatment alternatives (e.g. open surgery). After careful consideration of risk and benefits the investigator decided to proceed with direct visualization of the small bowel and adequate therapeutic inventions. Due to the non-interventional character of this study (i.e. registry) no additional protocol driven procedure besides medical standard are required. In summary the potential risk a subject enrolled into the SAMISEN study is considered identical to the risks he/she would be facing without participating in this study.

The complication rate associated with endoscopic procedures is usually low. Experience with deep enteroscopy of the small-bowel has been published for SBE and DBE. Distribution and incidence of complications depend whether it was a diagnostic or therapeutic approach. For therapeutic procedures tissue usually is removed or biopsies obtained which carries a higher complication rate compared to purely diagnostic procedures. A deep enteroscopy examination is performed with sedation or anesthesia, depending on the hospital standards. Any anesthesia carries a certain risk for the patient, especially if multi-morbidity is present.

Section 11.4 provides a list of all potential (S)AEs that have either been observed during or after deep enteroscopy with PowerSpiral conducted in a clinical study setting or are anticipated. There is no additional device related new risk identified that was not already anticipated for its predecessor.

The overall risk / benefit ratio for this clinical investigation is assumed to be in the same acceptable range of established balloon assisted methods of deep enteroscopy. As mentioned earlier this registry does not impose any additional “protocol driven” interventions or examinations therefore the procedural risk to which a patient will be exposed to should be very similar to the risk in case he/she would not have agreed to participate in this study

2 TRIAL OBJECTIVES

2.1 Objective

The main objective of this registry is to collect data on the safety and performance of the new motorized PowerSpiral device when used as intended by the manufacturer. It is assumed that the new device and its safety profile is non-inferior to preceding generations of balloon assisted enteroscopes.

As clinical performance and efficacy is equally important for the user this study also collects efficacy and handling data of the new device.

With this registry OLYMPUS complies with Post-Market Clinical Follow-up (PMCF) requirements.

3 DESIGN OF THE CLINICAL INVESTIGATION

3.1 General

3.1.1 Design Overview

SAMISEN is an international, multicenter, non-randomized, prospective, observational open label (registry) study examining the CE- marked PowerSpiral (OLYMPUS PSF-1, SINGLE USE POWER SPIRAL TUBE and motor control unit POWER SPIRAL CONTROL) device. (For justification of the study design please refer to section 1.2)

3.1.2 Randomization and Blinding or Assignment of Investigational Device

SAMISEN is designed as a prospective single-arm trial without control group or randomization. All subjects enrolled will undergo at least one procedure with the Motorized Spiral Endoscope (PowerSpiral). There may be a second (optional) procedure depending on investigator's discretion usually because the region of interest could not be reached during the first endoscopy. Subsequent endoscopic procedures are often characterized by a switch in direction (a first antegrade route may be followed by a second retrograde approach or vice versa). From a study perspective and because only part of the subjects will receive a second procedure this additional procedure is called "optional" to indicate that it is not required by protocol but will only be performed if considered necessary by the treating investigator.

3.1.3 Variables in the Clinical Investigation

It is a prospective and observational Registry without any additional procedure beyond clinical practice. The small-bowel enteroscopy has to be performed according the medical standard. Serious Adverse Events (SAE) and Device Deficiencies (DD) must be documented.

The main safety endpoint is a combined one, capturing all SAEs / DDs captured during the study period. The definition is:

- **Safety:** Incidence (% of subjects) and frequency (no. of subjects) of device or procedure related Serious Adverse Events (SAEs) and Device Deficiencies (DD) observed during/after the procedure.

As main efficacy endpoint we will determine in how many cases the suspected anatomical target lesion can be reached. The definition is:

- **Diagnostic Yield:** Defined as the percentage of procedures that either confirmed a diagnosis from previous studies, or established a new definitive diagnosis at the anatomical location identified in previous studies or findings that could explain the clinical symptoms (Sethi et al. 2014; Prachayakul et al. 2013; Lenz, Roggel, and Domagk 2013; Sanaka et al. 2012).

Further efficacy endpoints cover performance aspects of the device. The definitions are:

- **Therapeutic Yield**: Defined as the percentage of patients with any endoscopic intervention / therapy with the exception of biopsies. (Sethi et al. 2014; Prachayakul et al. 2013; Sanaka et al. 2012).
- **Total procedure time:** the time from oral (anal) insertion until withdrawal of the device.
- **Total therapeutic intervention time:** The part of the procedure dedicated to therapeutic maneuvers (biopsies will not be considered here).
- **Total small bowel enteroscopy rate:** Defined as complete evaluation of the small bowel either with a single approach or combined anterograde and retrograde approach (if complete small bowel enteroscopy is intended anyway (Committee et al. 2015; Gerson et al. 2015).
- **User feedback** and judgment of handling characteristics and other aspects.

3.1.4 Replacement of Subjects

If subjects enrolled into this study withdraw their consent or drop out for other reasons before the small-bowel enteroscopy was actually performed the site shall continue to enroll subjects and conduct enteroscopies until the quota of 22 “subjects counting” for the site has been completed. Besides that, it is not foreseen to replace subjects that drop out after the first enteroscopy but before hospital discharge.

3.2 Investigational Device(s) and Comparators

3.2.1 Investigational Device(s)

In this prospective Registry all investigators will deploy a motorized PowerSpiral device. There are no different (sub)types of this devices, so all devices used will be identical.

3.2.2 Comparator Devices(s)

Not applicable.

3.2.3 Reference Device(s)

Balloon assisted enteroscopy (BAE) devices used for deep enteroscopy and as described in the literature (Rondonotti et al. 2018) will serve as historical controls.

3.2.4 Other Medical Device / Medication

Not applicable.

3.3 Subjects

3.3.1 Inclusion criteria

In order to be considered eligible for participation in this investigation subjects must meet all of the inclusion criteria listed below:

- Signed informed consent
- Patients with small bowel disease indicated for deep enteroscopy, including but not limited to:
    - Gastrointestinal bleeding
    - Crohn's disease
    - Abdominal pain or chronic diarrhea
    - Large polyps (>10–15mm) in the jejunum and ileum in patients with Peutz–Jeghers syndrome
    - Nonresponsive or refractory coeliac disease
    - Results and hints from other preliminary investigations, e.g. small-bowel capsule endoscopy, small-bowel imaging examinations etc. which warrant further work-up with antegrade and/or retrograde enteroscopy of the small-bowel.

3.3.2 Exclusion criteria

In addition to be eligible for study enrollment a subject must **not** meet any of the exclusion criteria listed below:

- Age under 18 years
- Female and of child-bearing age who is currently pregnant or planning to become pregnant within the study period
- Any contraindication to standard enteroscopy (e.g. severe coagulopathy or known coagulation disorder; bowel obstruction / stenosis, stents or other instruments implanted in the intestinal tract, suspected GI perforation, esophageal or gastric varices, eosinophilic esophagitis) as judged by the investigator after careful individual risk assessment
- Concurrent participation in another competing clinical study

3.3.3 Subject Withdrawal or discontinuation

A subject may withdraw his/her consent to participation at any time without explanation and without consequences for further treatment. Moreover, the study treatment may be discontinued temporarily or permanently due to one of the following reasons:

1. Any health deterioration of the subject, e.g. ALAT and/or ASAT > 3 times upper limit of normal range,
2. Not acceptable further study participation as determined by the investigator,
3. Occurrence of not tolerable adverse events and/or laboratory value alterations,
4. Technical reasons (change of physician, change of address of subject),

5. Lacking compliance of subject,
6. Pregnancy,
7. Major CIP deviation,
8. Subject lost to follow-up,
9. Death.

If a subject discontinues participation in the study after signing the consent for whatever reason, every effort has to be made to perform an early termination visit in case the antegrade and/or retrograde examination were already conducted. In this case, the same examinations as in the final visit (Visit 4) shall be performed.

3.3.4 Point of Enrolment

Point of enrolment is defined as the time at which a subject dates and signs the informed consent. At least one day prior to that, the investigator shall provide a complete explanation of the study (benefits, risks, rights and obligations).

3.3.5 Duration of the Clinical Investigation

The average duration of study participation for subjects completing the study is estimated to be approximately 2 days up to one week. It depends among others if only a single enteroscopy is planned or a combined antegrade and retrograde approach at two examination days. The estimated total study duration for the whole study cohort is approximately one year. The end of study is defined as the date of the database lock.

3.3.6 Sample size

A total of 260 subjects shall be enrolled into this registry. This number factors in an expected drop-out-rate of 5%. Taking into account a drop-out-rate of 5% data from a total of 245 patients is expected to be available for statistical endpoints analyses.

With a sample size of 245 patients, the SAE rate can be estimated with a precision (i.e. width of the 95% confidence interval for the SAE rate) as shown in the following table.

Table 1 Precision of estimations of the rate of patients with at least one SAE

Sample size N	Patients with SAE	Rate of patients with SAE	95% CI (Clopper-Pearson)
245	5	2.0%	0.7% - 4.7%
245	10	4.1%	2.0% - 7.4%
245	15	6.1%	3.5% - 9.9%
245	20	8.2%	5.1% - 12.3%
245	25	10.2%	6.7% - 14.7%
245	30	12.2%	8.4% - 17.0%

As historical control, a SAE rate of 8% is considered (upper limit of the accepted SAE rate for patients undergoing deep enteroscopy according to the guideline (Rondonotti et al. 2018)).

In addition, to reflect the learning curve of each individual investigator, the first 5 patients per investigator will be considered training patients to become familiar with the handling and usage. All information of these “training patients” will be documented in the eCRF. These will be analyzed separately. 12 clinical sites in Germany, Belgium, France, Netherland, Italy, Denmark, Norway and Finland will be approached. At each site there will be either one or two investigators. Based on current information there will be approx. 15 investigators participating. Adding patients from the learning curve (15 x 5 = 75) and the 260 study patient’s counting towards the endpoints together this study will enroll approximately 335 patients in total.

The enrolment period starts in May/June 2019 and will stop once the expected number of patients per site is reached. This “Last-Patient-In” (end of recruitment) is expected in May/June 2020.

Each site with two investigators shall take every effort to enroll a balanced number of patients per investigator.

Statistical Analyses will be performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3.4 Procedures

3.4.1 Overview of the Procedures and Laboratory Measurements

Table 2 gives an overview of the relevant study procedures:

Table 2 List of study procedures

Visit	**V1**	**V2**	**V3**	**V4**
	Screening	**1st scheduled procedure**	**2nd scheduled procedure (optional)**	**Hospital discharge visit**
Patient informed consent	**x**			
Inclusion/Exclusion criteria	**x**			
Demographic data	**x**			
Physical examination with vital signs, body measurements (body weight and body height) and concomitant diseases	**x**			
Small-bowel enteroscopy with PowerSpiral		**x**	**x**	
Evaluation of criteria regarding usage of PowerSpiral		**x**		
(Serious) Adverse Events		**x**	**x**	**x**

3.4.2 Description of clinical investigation related procedures and assessed data

At the screening visit the investigator informs the patient about the trial and selects the patient as potentially suitable for this trial. The patient should receive the patient information and patient consent sheet for information. An official Visit 1 will be arranged.

The following data will be collected during the clinical investigation at the various study visits:

At visit V1:

At this visit the patient will be informed about the trial in detail and the patient consent must be signed at Visit 1 (or earlier). All questions of the patient shall be answered.

The following data shall be captured for all patients meeting the inclusion and exclusion criteria:

- Demographic Data
  - Age
  - Sex
- Physical Examination
  - Height
  - Weight
  - Radial pulse (with the subject in the supine position for at least 5 minutes before).
  - Blood pressure (according to Riva Rocci using calibrated sphygmomanometers, the subject has to be in a sitting position for at least 5 minutes, blood pressure will be measured twice within 5 minutes, the mean of both measurements will be calculated).
  - Document if a 12-lead ECG was recorded as medical standard in your hospital.
  - Document if a clinical standard panel of laboratory parameters is determined prior to small-intestine enteroscopy as medical standard in your hospital. Any deviation of laboratory parameters exceeding normal ranges shall be documented and followed up, as appropriate. Clinically significant deviations observed during the screening visit and throughout the study will be documented in the Case Report Form.
  - Select the appropriate ASA class[1] [1] to assess the fitness of the patient.
  - Document any abnormalities detected in one of the following organ systems:
    - Head, neck and thyroid (gland)
    - Skin and mucosa
    - Cardiovascular system
    - Respiratory system
    - Abdomen
    - Spine
    - Extremities
    - Reflexes
    - Other
- Provide information about the following concomitant medication
  - Acetylsalicylic acid

[1] We recommend to take the ASA class from the anesthesiologic pre-medication records

- Anticoagulant therapy
- Discontinuation of Anticoagulant therapy prior / during the procedure

- Provide information about the planned small-bowel enteroscopy
  - Main indication for the planned small- bowel enteroscopy procedure.
  - Select if a capsule endoscopy, CT/MRT enteroclysma or another imaging technique was performed previously.
  - Describe if there were any positive findings during the previous diagnostic workup (e.g. if a bleeding was detected).
- Describe the initially planned PowerSpiral approach
  - Is a total enteroscopy of the small-bowel planned?
  - Start with antegrade procedure and add a retrograde one if unsuccessful or incomplete *or*
  - Start with retrograde procedure and add an antegrade one if the initial procedure is unsuccessful or incomplete *or*
  - Perform a combined antegrade and retrograde examination during a single session.

At visit V2 and V3 (optional):

- At this visit the PowerSpiral enteroscopy will be performed.
- Enter the date and name of the responsible investigator who performs the enteroscopy.
- Enter the total procedure time (“scope-in, scope-out”) measured from initial enteroscope introduction through the bite block to final enteroscope withdrawal through the bite block (minutes) (for antegrade approach) or crossing the linea dentata of the anus in case of a retrograde approach.
- Provide information about the kind of staff and number persons needed for this enteroscopy.
- Select if an antegrade, retrograde or combined enteroscopy was performed.
- Select if a general anesthesia or sedation is used.
- Select which part of the small-bowel was reached.
- Answer if the findings of the previous imaging examinations were confirmed or not.

- Answer if there was any therapeutic intervention performed. If yes please specify in the free text section.
- Enter the time needed for any therapeutic intervention. If several slots for therapeutic interventions occurred, please add the time needed for each therapeutic slot and enter the total duration in minutes.
- Answer if any Serious Adverse Events occurred during the enteroscopy procedure.
- Document the final diagnosis after the enteroscopy
- Answer the following questions:
    - Was the therapeutic intervention successful and were all planned therapeutic aim(s) achieved?
    - Was the initial therapeutic management plan modified during the procedure?
    - Was total enteroscopy achieved?
    - Do you plan for another enteroscopy?

After visit 2 the investigator shall give an evaluation of the PowerSpiral procedure in comparison to BAE medical devices for deep enteroscopy previously used. The investigator shall judge if the PowerSpiral is “worse”, “similar” or “better” than previous equipment used for the following topics:

- **Handling** (Handling means the whole handling of the instrument (PowerSpiral scope + overtube + motor control unit) during preparation of the equipment and throughout the examination).
- **Instrument insertion** (Instrument insertion means how the instrument could be inserted either in the antegrade or retrograde route (whichever was selected).
- **Precision of positioning during therapy** (This means how precise and how stable the instrument could be positioned during a therapeutic intervention).
- **Time needed for procedure** (It means the time duration describes the start as entering the endoscope in the mouth or anus until withdrawal which suppose as stop point).
- Staff and resources required for procedure.

Visit 3 is a second (optional) procedure depending on investigator’s discretion.

In case the investigator plans a second approach a tattoo or clip should be set at the deepest part of the small-bowel before the investigator starts the withdrawal of the PowerSpiral.

At visit 4

Visit 4 is the hospital discharge visit. The patient is ready to leave the hospital and the status shall be documented.

The following data will be documented:

- Date of the hospital discharge examination.
- Actual discharge date.
- if the patient has recovered from the examination.
- Describe new (Serious) Adverse Event if any
- Clinical signs or symptoms of pancreatitis e.g. elevated Lipase/Amylase (if measured post-procedure as medical standard in your hospital).
- Specify if the patient get further treatment from the referral physician or if additional specialist(s) will be involved.

The investigator will ensure that the patient receives further medication as necessary and can be discharged from hospital and consigned to GP's or medical specialist's care.

Finally, the investigator shall to sign off the eCRF to confirm that the data is complete and accurate.

3.4.3 Study Visits Schedule

After visit V1 the investigator will schedule the antegrade or retrograde or combined enteroscopy depending on investigator's discretion. There are no predetermined time intervals between V1 and V2 or V2 and V3. Also the standard preparation procedure in your hospital for defecation before small-bowel enteroscopy shall be followed as usual.

The small-bowel enteroscopy duration depends on the individual diagnostic and treatment activities for each patient. Approximately 45 min are assumed for an uncomplicated antegrade examination.

The final visit V4 shall be completed prior to hospital discharge.

Premature study discontinuation of a study subject is to be noted as such on the case report form (eCRF).

3.4.4 Concomitant treatments

Concomitant treatment during study participation should be in line with the medical standard for small-bowel enteroscopy. Information about Acetylsalicylic acid and Anticoagulant therapy must be documented in the eCRF.

3.4.5 Medical Care after Termination of the Clinical Investigation

At the final visit V4 the investigator will ensure that the patient can be discharged from hospital without any identifiable risk and that further treatment on an outpatient basis through a general practitioner or medical specialist will be provided as necessary. Any ongoing (serious) adverse events that deserve special attention shall be mentioned in the patient's discharge letter.

3.4.6 Deviations from medical standard

The observational character of this registry study does not require any additional clinical procedure or tests beyond standard of care. Any deviation for medical reasons shall be documented in the eCRF.

3.5 Monitoring Plan

3.5.1 Responsibilities

Study monitoring will be performed by the [redacted]

The monitor will visit the study sites in order to check that eCRFs are completed without omission, and that Good Clinical Practice guidelines and the CIP are followed. He/she will also check the progress of subject inclusion. The monitor shall be granted access to the study binder and hospital records of enrolled subjects. The study nurse shall be available to the monitor during monitoring visit(s). The investigator is expected to be available at least for a debriefing at the end of the monitoring site visit.

After study end the site will receive a copy of the eCRF file and the investigator has to ensure that it is stored safely with all other study documents filed in the Investigator Site File according to national law.

3.5.2 Source Data Definition and Verification (SDV)

Source data are the original records of all variables collected for the clinical investigation. They include, but are not limited to:

- Signed informed consent,
- Laboratory reports,
- Individual subject clinical notes,
- Hospital charts or pharmacy records and any other similar reports and records of any procedure performed in accordance with the CIP,
- Details concerning inclusion and exclusion criteria.

The investigator must allow the monitor access to all documents in the medical file to confirm their consistency with the electronic case report form entries. All information entered in the eCRF must be available as source data. No information about subject identity on these documents will

be allowed to leave the study site. At a minimum the following points will be verified by the monitor: existence of signed informed consent, adherence to inclusion/exclusion criteria, all SAEs and a tabulation of adverse events. Further checks may be carried out according to the study specific monitoring plan to confirm matching of all eCRF data matches source data.

For more details on Monitoring of this Clinical Investigation please refer to the “Monitoring Plan” (available upon request).

4 STATISTICIS

Statistical analysis of the data will be performed by [redacted]. The evaluation will be specified in the Statistical Analysis Plan (SAP) laid down in a separate document.

Demographic data, baseline characteristics and information of the physical examination and medical history with concomitant medication will be reported in summary tables. Additional information about the planned small-bowel enteroscopy will be reported.

4.1 Statistical methods

4.1.1 Background and demographic characteristics

Continuous variables such as age will be presented by mean, standard deviation, minimum, median and maximum. Categorical data such as gender will be presented as absolute and relative frequencies.

All variables with no coding available will be listed.

4.1.2 Efficacy evaluation

The efficacy endpoints are defined as follows:

- **Reaching the anatomical region of interest**: The rate of successfully reaching the suspected anatomical target region (either by antegrade or by retrograde route) compared to all attempts represents the **anatomical success rate**.
- **Therapeutic Yield**: Defined as the percentage of patients with any endoscopic intervention / therapy with the exception of biopsies. (Sethi et al. 2014; Prachayakul et al. 2013; Sanaka et al. 2012).
- **Total procedure time.**
- **Total therapeutic intervention time:** period in min dedicated to therapeutic intervention(s)**.**
- **Total small bowel enteroscopy rate:** Defined as complete evaluation of the small bowel either with a single approach or combined anterograde and retrograde approach (if complete small bowel enteroscopy is intended anyway (Committee et al. 2015; Gerson et al. 2015).
- **User feedback** and judgment of handling characteristics and other aspects.

- User feedback and assessment of handling characteristics and other logistical aspects regarding:
    - Handling of PowerSpiral
    - Instrument insertion of PowerSpiral
    - Precision of positioning during therapy of PowerSpiral
    - Time needed for procedure of PowerSpiral
    - Staff and resource needed for procedure of PowerSpiral

No hypothesis testing will be performed for any efficacy endpoint.

4.1.3 Safety evaluation

The following safety variables will be collected:

- Serious adverse events during and after enteroscopy procedure
- Serious adverse events (procedure or product related)
- Adverse events during enteroscopy procedure

The safety variables will be tabulated for all study participants.

Adverse events data will be processed in the statistical analysis after coding.

AEs and device deficiencies will be presented in summary tables. These tables will show the number of subjects per group presenting an adverse event and the incidence of its occurrence. Adverse events will be grouped by system organ class and stratified by severity (mild, moderate, severe) and by relation to study treatment (unrelated or related according to the categories definite, probable and possible).

4.1.4 Interim analysis

Not planned.

4.1.5 Other evaluations

Not planned.

4.2 Subgroup Analyses

No subgroup analysis planned.

4.3 Missing/spurious Data

All available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified there will be no substitution of missing data, i.e. missing data will not be replaced, missing data will be handled as 'missing' in the statistical evaluation.

5 DATA MANAGEMENT

5.1 Data recording

Data shall be recorded in the eCRFs in a timely manner but not later than 5 working days after collection of the data, including signatures. Please take into account, a SAE must be documented immediately to meet the reporting requirements. The investigator must document all visits and assessments on the respective eCRF form and shall ensure that no empty data blocks exist. If a test or assessment was not performed, the investigator shall indicate this. If a question does not apply, the investigator shall also document this (e.g. by entering “NA”).

The investigator shall sign the overall affirmation statement for each patient to document personal responsibility for accuracy, completeness of data captured in the system and for the trial being carried out according to the protocol and any amendments.

Data can only be entered by authorized and trained site staff, i.e. by the investigator or investigator’s staff trained on eCRF procedures. (S)AE pages must be signed off by the investigator.

Data corrections in the eCRF done by the investigator or designee require entering a reason for the data change. The change of already entered data and the person who performed the data change will be tracked in the audit trail of the eCRF. In case of data changes in the eCRF that has already been signed off a new signature is required to authorize the data modification.

Queries issued within the eCRF shall be answered within 7 working days.

5.2 Data processing

Data processing, controls of plausibility and query handling will be carried out by the [redacted]. The study database will be created according to the format and content of the eCRF and the CIP. The ICD-10 code will be used for coding of adverse events and previous / concomitant diseases.

6 AMENDMENTS TO THE CIP

CIP amendments or supplements (apart from minor administrative changes) require a written amendment. Amendments must be approved by the EC and the regulatory authorities, if locally applicable, before implementation. A copy of the written approvals will be provided to the investigators.

The following list provide an overview about the changes compare to CIP version no. 01 from 20. December 2018.

Table 3 List of changes CIP version 01 versus CIP version 02.

Amend-ment no. 01	Section	Previous version CIP version 01 from 20th Dec 2018	Changed Version CIP version 02 from 23 April 2019
	Trial summary / endpoints	**Endpoints** …. • **Endoscopic** and **ERCP success rates** in patients with altered upper GI anatomy (e.g. Roux-en-Y gastric bypass).	**Endpoints** …… • **Endoscopic success rates.**
	Trial summary/Study Population	**Inclusion criteria** **1.** Signed informed consent **2.** Patients with small bowel disease indicated for deep enteroscopy, including but not limited to: • Gastrointestinal bleeding • Crohn's disease • Abdominal pain or chronic diarrhea • Large polyps (>10–15mm) in the jejunum and ileum in patients with Peutz–Jeghers syndrome • Nonresponsive or refractory coeliac disease • Results and hints from other preliminary investigations, e.g. small-bowel capsule endoscopy, small-bowel imaging examinations etc. which warrant further work-up with antegrade and/or retrograde enteroscopy of the small-bowel. or • Patients with altered upper GI anatomy (e.g. Roux-en-Y or BII) indicated for	**Inclusion criteria** **1.** Signed informed consent **2.** Patients with small bowel disease indicated for deep enteroscopy, including but not limited to: • Gastrointestinal bleeding • Crohn's disease • Abdominal pain or chronic diarrhea • Large polyps (>10–15mm) in the jejunum and ileum in patients with Peutz–Jeghers syndrome • Nonresponsive or refractory coeliac disease • Results and hints from other preliminary investigations, e.g. small-bowel capsule endoscopy, small-bowel imaging examinations etc. which warrant further work-up with antegrade and/or retrograde enteroscopy of the small-bowel.

		ERCP where access with conventional ERCP devices is of no avail and after careful individual risk assessment	
	1 BACKGROUND AND RATIONALE	Small bowel enteroscopy is usually performed in order to evaluate gastrointestinal bleeding, small bowel tumors, polyps, inflammatory or other small bowel diseases. Video capsule endoscopy, single- (SBE), double-balloon (DBE) or spiral enteroscopy are the most popular non-surgical endoscopic techniques in this context. Hereof the endoscopic approach offers additional diagnostic and therapeutic options as biopsies and direct therapeutic intervention is possible compared to capsule endoscopy. These enteroscopy systems – also called overtube-assisted enteroscopy (OAE) techniques - are used to visualize the small-bowel and proceed with a therapeutic intervention, either during the same or in a subsequent session. For example the DBE utilizes distal and proximal balloons that can be inflated and deflated to “anchor” and move the bowel, thereby assisting the operator in advancing the endoscope while gathering the bowel onto the overtube shaft. However, the SBE and DBE procedures are time consuming and usually require 2 operators to perform this kind of examination. Patients with altered upper gastrointestinal (upper GI) anatomy (such as Roux-en-Y gastric bypass) indicated for endoscopic retrograde cholangiopancreatography (ERCP) represent a special challenge to the investigator. The new endoscopic techniques originally designed for deep enteroscopy have increased the potential to reach the area of interest and successfully perform ERCP and therapeutic interventions at acceptable complication rates (Skinner et al. 2014). This has led to increasing acceptance of OAE techniques in this special patient cohort.	Small bowel enteroscopy is usually performed in order to evaluate gastrointestinal bleeding, small bowel tumors, polyps, inflammatory or other small bowel diseases. Video capsule endoscopy, single- (SBE), double-balloon (DBE) or spiral enteroscopy are the most popular non-surgical endoscopic techniques in this context. Hereof the endoscopic approach offers additional diagnostic and therapeutic options as biopsies and direct therapeutic intervention is possible compared to capsule endoscopy. These enteroscopy systems – also called overtube-assisted enteroscopy (OAE) techniques - are used to visualize the small-bowel and proceed with a therapeutic intervention, either during the same or in a subsequent session. For example, the DBE utilizes distal and proximal balloons that can be inflated and deflated to “anchor” and move the bowel, thereby assisting the operator in advancing the endoscope while gathering the bowel onto the overtube shaft. However, the SBE and DBE procedures are time consuming and usually require 2 operators to perform this kind of examination.
	1.2. Justification for the	… For the same reason inclusion criteria are kept as broad as possible.	…. For the same reason inclusion criteria are kept as broad as possible. In

	Design of the Clinical Investigation	In summary all patients are eligible where the physician realizes an indication for deep enteroscopy for further diagnostic or therapeutic work up. In patients with altered upper GI anatomy, such as e.g. Roux-en-Y gastric bypass indicated for ERCP is in line with the intended use and hence can be performed using PowerSpiral if deemed appropriate by the investigator. So inclusion of these patients into this registry is possible. The exclusion criteria will only affect patients under the age of 18 years and pregnant women. Otherwise clinical judgement of the treating physician is the only relevant and leading reason for exclusion. Of course giving signed informed consent by all study subjects is a prerequisite for participation in this "registry".	summary all patients are eligible where the physician realizes an indication for deep enteroscopy for further diagnostic or therapeutic work up. The exclusion criteria will only affect patients under the age of 18 years and pregnant women. Otherwise clinical judgement of the treating physician is the only relevant and leading reason for exclusion. Of course giving signed informed consent by all study subjects is a prerequisite for participation in this "registry".
	3.1.3 Variables in the Clinical Investigation	…… • **Total small bowel enteroscopy rate:** Defined as complete evaluation of the small bowel either with a single approach or combined anterograde and retrograde approach (if complete small bowel enteroscopy is intended anyway (Committee et al. 2015; Gerson et al. 2015). • **User feedback** and judgment of handling characteristics and other aspects. • For "ERCP patients" [2]only: ○ **Endoscopic Success Rate**: defined as the percentage of procedures in which the investigator was able to reach the major papilla or the biliodigestive or pancreatic anastomosis when ERPC was planned. ○ **ERCP Success Rate:** defined as the	…….. • **Total small bowel enteroscopy rate:** Defined as complete evaluation of the small bowel either with a single approach or combined anterograde and retrograde approach (if complete small bowel enteroscopy is intended anyway (Committee et al. 2015; Gerson et al. 2015). • **User feedback** and judgment of handling characteristics and other aspects.

[2] Patients with altered upper GI anatomy now indicated for ERCP with PowerSpiral as judged by the investigator

		percentage of therapeutic interventions successfully completed by the investigator. ○ **Total procedure time**, **safety** related aspects and **user feedback** will be collected as described above.	

	3.3.1 Inclusion criteria	In order to be considered eligible for participation in this investigation subjects must meet all of the inclusion criteria listed below:
		• Signed informed consent
		• Patients with small bowel disease indicated for deep enteroscopy, including but not limited to:
		  • Gastrointestinal bleeding
		  • Crohn's disease
		  • Abdominal pain or chronic diarrhea
		  • Large polyps (>10–15mm) in the jejunum and ileum in patients with Peutz–Jeghers syndrome
		  • Nonresponsive or refractory coeliac disease
		  • Results and hints from other preliminary investigations, e.g. small-bowel capsule endoscopy, small-bowel imaging examinations etc. which warrant further work-up with antegrade and/or retrograde enteroscopy of
			In order to be considered eligible for participation in this investigation subjects must meet all of the inclusion criteria listed below:
			• Signed informed consent
			• Patients with small bowel disease indicated for deep enteroscopy, including but not limited to:
			  • Gastrointestinal bleeding
			  • Crohn's disease
			  • Abdominal pain or chronic diarrhea
			  • Large polyps (>10–15mm) in the jejunum and ileum in patients with Peutz–Jeghers syndrome
			  • Nonresponsive or refractory coeliac disease
			  • Results and hints from other preliminary investigations, e.g. small-bowel capsule endoscopy, small-bowel imaging examinations etc. which warrant further work-up with antegrade and/or retrograde enteroscopy of the small-bowel.

		the small-bowel. or • Patients with altered upper GI anatomy (e.g. Roux-en-Y or BII) indicated for ERCP where access with conventional ERCP devices is of no avail and after careful individual risk assessment	
	3.4.2 Description of clinical investigation related procedures and assessed data	**At visit V2 and V3 (optional):** • At this visit the PowerSpiral enteroscopy will be performed. It is recommended to plan and perform an ERCP procedure only after the individual investigator's learning curve (patient #1 to #5) has been completed.	**At visit V2 and V3 (optional):** At this visit the PowerSpiral enteroscopy will be performed.
	4.1.2 Efficacy evaluation	• For "ERCP patients" only: ○ **Endoscopic Success Rate**: defined as the percentage of procedures in which the investigator was able to reach the major papilla or the biliodigestive or pancreatic anastomosis when ERPC was planned. ○ **ERCP Success Rate:** defined as the percentage of therapeutic interventions successfully completed by the investigator ○ **Total procedure time**, **safety** related aspects and **user feedback** will be collected as	-/-

		described above	
	4.2 Subgroup Analyses	Patients indicated for ERCP with PS will be analyzed separately.	No subgroup analysis planned.
	7.1. CIP deviation	Major CIP deviations are, but are not restricted to • Deviation from the in- and exclusion criteria • Performing ERCP before the individual learning curve (5 PS procedures performed as deep enteroscopy) has been completed.	Major CIP deviations are, but are not restricted to • Deviation from the in- and exclusion criteria

7 CIP DEVIATIONS

The investigator must not deviate from the procedures described in this CIP.

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations must be documented and reported to the sponsor and the EC as soon as possible.

Classifications into minor and major CIP deviations will be performed by the clinical operations manager and statistician at the end of the study.

Major CIP deviations are, but are not restricted to

- Deviation from the in- and exclusion criteria

8 DEVICE ACCOUNTABILITY

This study is a post-market study. The PS enteroscopes are CE-marked. Hence from a regulatory perspective strict device accountability is not needed. However, the sponsor will have a list of serial numbers and can track which device was delivered to which study site.

The devices are usually purchased by the site. Olympus will provide devices as loaner equipment to a limited number of sites serving as centers of excellence. Any loaner equipment shall be exclusively used for the examination of study patients. After reaching the agreed quota per site (5 learning curve patients per investigator + 22 subjects counting towards the endpoints) the device must be returned to Olympus. Details are specified in the Clinical Trial Agreements.

9 STATEMENT OF COMPLIANCE

9.1 Ethical and Regulatory Aspects

The clinical investigation will be carried out in accordance with the following texts:

- The Declaration of Helsinki (1996)
- Good Clinical Practice (ICH E6) (current version)
- DIN EN ISO 14155:2011

The clinical investigation will not begin until the required approval / favorable opinion from the EC and / or regulatory authority (if applicable) have been obtained. Any additional requirements imposed by the EC or regulatory authority will be followed.

Regulatory reporting responsibilities are specified in the respective Clinical Trial Agreements that also need to be duly signed prior to the first enrollment.

Quality Control and Quality Assurance systems will ensure that the clinical investigation is conducted according to local law and Good Clinical Practices. Olympus Europa SE & Co. KG will follow their own Standardized Operating Procedures covering all aspects of the clinical investigation.

9.2 Patient Coverage

The PowerSpiral medical device is a CE-certified and CE-marked product. Any patient product liability claims will be covered in accordance with the applicable product liability law. Additional patient coverage will be provided by the sponsor if required by national law.

9.3 Retention of Documents

The investigator must conduct the study in compliance with the Medical Devices Act and Good Clinical Practices. The study documents comprise the following:

- Case report forms,
- Data correction/clarification forms,
- Source documents,
- Correspondence between sponsor/CRO and investigator,
- Regulatory documents such as:
    - Signed CIP and any amendments,
    - EC approval and correspondence,
    - Curriculum Vitae of medical personnel (investigators, study nurses, etc.),
    - Subject signed consent forms,

- Investigator's contract

Source documents for study subjects shall be marked with the CIP Reference number **[2018-GI (OEKG) -01]**.

The CIP, case report forms, correspondence, original informed consent forms, subject identification log with names of the patients and other documents concerning the study must be kept by the investigator in the investigator site file according to local regulations. The safekeeping period is usually 15 years after study close-out.

9.4 Auditing procedures

National or foreign Health authorities may want to inspect your site at any time during or after the study. By participating in this clinical investigation investigators agree to and will grant authorized inspectors access to all original documents, including subject files. If subject files or medical records are stored on a computer system, the investigator (or delegate) shall ensure that data requested by the inspector is printed on paper, dated and signed before handed over to the inspector. Inspectors do not have direct access to the sites computer system.

Also the sponsor (Olympus Europa SE & Co. KG) reserves the right to perform an audit during the active study phase or after study closeout.

10 INFORMED CONSENT

Before enrolment in the clinical investigation, the investigator must make sure that all eligible subjects are well provided with detailed information, both orally and in writing, about the following points in particular:

- Aims, duration and methods of the clinical investigation.
- Risks, anticipated benefits and potential hazards according to current knowledge.
- That he/she is free to withdraw his/her consent at any time without affecting subsequent treatment or his/her relation to the physician.
- That the clinical research monitors and auditors, Health Authority Inspectors and EC/IRB members may have access to their clinical source data.

Informed consent must be given by a standard written declaration drafted in simple non-technical language. Subjects will also be informed that the data collected during the study will be archived and processed in accordance with local individual data protection law.

The subject must read and understand the contents of this form before signing and dating it. He/she has to be provided with a signed version. No subject may be enrolled in this clinical investigation before giving his/her informed consent in writing.

The investigator will inform all subjects included in the clinical investigation about any new information on the investigational device discovered during the study, in accordance with the recommendations of Olympus Europa SE & Co. KG, the sponsor, and the EC.

The investigator must hold an updated list of all subjects enrolled in the study by recording their subject number. A Subject Identification Log Template will be provided by the sponsor.

11 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

11.1 Definitions (according to ISO 14155:2011)

11.1.1 Adverse event (AE)

The term AE describes any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including laboratory values) in subjects, users or other persons, whether or not related to the investigational medical device. For subjects this definition includes:

- Events related to the investigational medical device
- Events related to the procedures involved
- For users or other persons, this definition is restricted to events related to investigational medical devices

Note:

A “significant deterioration in laboratory parameters“ means an abnormal lab value, which is deemed clinically significant when any of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g. change of treatment, discontinuation of treatment, close observation, more frequent follow-up assessments, or further diagnostic investigation.

Therefore, a clinically significant deterioration of a lab value is one that indicates a new disease process, worsening of an existing condition, or requires further action(s) to be taken.

11.1.2 Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device.

Note:

- This definition includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
- This definition includes any event that is a result of a use error or intentional misuse.
- This includes medical devices already on the market that are being evaluated for unintended uses, new populations, new materials or design changes.

11.1.3 Serious Adverse Event / Serious Adverse Device Effect (SAE /SADE)

A SAE/SADE is further specified by the fact that it results or could have resulted in death or severe deterioration of health of a subject, user, or other persons, whether (SADE) or not (SAE) related to the investigational medical device.

The criteria for a Serious Adverse Event (SAE) are the following:

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

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

The following points should be taken into account when evaluating the seriousness of an Adverse Event:

- The life-threatening criterion indicates that there was an immediate risk of death at the time of its occurrence. This does not mean that if the adverse event had occurred in a more severe form it would have led to death.
- The following events are not considered to be serious adverse events:
    - An event causing a brief visit to a hospital consultation, an open-door or day hospital.
    - Outpatient treatment in the emergency department although the reason for which this treatment was instituted may be serious.
    - Admission to hospital (more than one night in a hospital bed) including surgical operations planned before or during the study if the condition was present before the study and provided that it does not worsen during the study.

Note:

A state of pregnancy is an exclusion criterion. Hence contraceptive measures must be taken by all subjects of childbearing potential throughout the study. However, if pregnancy is discovered during the study, the study participation must be discontinued immediately and the outcome of the pregnancy must be followed up carefully. Any abnormal outcome of the child or the mother must be documented.

11.1.4 Device Deficiencies

Device Deficiencies means any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

11.2 Documentation

11.2.1 (Serious) Adverse Events / Adverse Device Effects

Independent from a possible relation to the investigational device, every AE spontaneously reported by the subject or observed by the investigator has to be reported on the appropriate page of the case report form. Furthermore, the investigator shall actively ask the subject about the occurrence of any (S)AE at each visit and note any abnormal laboratory findings. For each adverse event the following information should be documented:

- Description of the event (diagnosis and symptoms in verbatim terms),
- Outcome,
- Seriousness,
- Duration (start date and stop date),
- Causal relationship to the investigational device.
  Causality assessment will be done by the investigator using a 5-category system (no related / unlikely / possible / probable / causal relationship).
- Any therapy or corrective action initiated including.

The results of any complementary tests performed (laboratory tests, ECG, etc.) must be pseudonymized by the investigator prior to forwarding information to the sponsor. A period of 4 weeks for follow up of AEs after the subject has routinely completed or prematurely terminated the study seems sufficient. This means that any additional information needed to assess the (S)AE should be collected and documented in the respective CRF within one month after occurrence.

11.2.2 Device deficiencies

Two device deficiencies of the disposable Spiral Segment were documented in previous clinical studies with PowerSpiral. The technical issues are addressed and solved.

11.3 Reporting Responsibilities

11.3.1 Serious Adverse Events (SAE) / Serious Adverse Device Effects (SADE)

After the signature on the consent form is obtained, any SAE occurring while the subject is enrolled in the study must be immediately reported by the investigator.

11.3.1.1 Serious Adverse Event - Initial Report

The investigator has to report every SAE immediately after he/she becomes aware of the SAE.

The Sponsor compile an accumulated SAE list and share with Ethical Committees on a bi-annual basis (if requested by the respective Ethical Committees). However, for international safety reporting requirements the sponsor needs to be informed immediately about any observed SAE.

11.3.1.2 Serious Adverse Event - Follow-up Report

If the event / SAE is not resolved further information (e.g. laboratory reports, surgical reports) for full assessment is needed and shall be provided as soon as it becomes available. The sponsor may request additional documents, shall be provided within 5 days.

11.3.2 Device deficiencies

Device deficiencies shall be reported to the sponsor not later than 7 working days after observation.

11.3.3 Responsible Nominated Safety Contact

[redacted]

11.4 Anticipated Adverse Events

Foreseeable risks include those typically associated with deep enteroscopy performed under general anesthesia or sedation.

The following device and process related events were observed in previous Investigator-Initiated-Trials with PowerSpiral. The SAMISEN study will contribute and extend the safety profile of the PowerSpiral device.

Table 4 List of anticipated (Serious) Adverse Events

- mucosal damage
- mucosal abrasion
- mucosal inflammation
- bleeding
- hematoma
- perforation
- infection
- pain (such as abdominal pain and sore throat)
- abdominal distention
- discomfort (such as abdominal discomfort and swallowing discomfort)
- digestive dysfunction (such as indigestion, nausea, vomiting)
- cardiovascular problem (bradycardia, tachycardia, hypotension and hypertension)
- dysphagia (such as odynophagia)
- respiratory system disorder (such as aspiration pneumonia, cough, hypoxemia and mediastinal emphysema)
- pancreatitis
- fever
- hyperamylasemia
- hyperlipasemia
- intestinal obstruction
- intestinal necrosis
- intussusception
- parotitis
- hiccup
- electrification
- burn
- foreign body retention
- intoxation
- gas embolism
- mucosal paratripsis
- cut

11.5 Data Monitoring Committee

Not applicable.

12 VULNERABLE POPULATION

It is not planned to include a vulnerable population.

13 SUSPENSION OR PREMATURE TERMINATION

Certain circumstances may lead to early termination of an entire clinical investigation, in particular for ethical or safety reasons such as:

- The high frequency and/or unexpected severity of adverse events.
- Unsatisfactory recruitment of subjects as far as their quantity or quality is concerned or recurrent incomplete/inappropriate collection of data.

The decision to put a study on hold or for premature termination will be made by the Sponsor.

14 PUBLICATION POLICY

The sponsor is explicitly committed to publish the trial results in a scientific medical journal and / or presented at scientific meetings. The Investigator agrees that any publication by the Study Site of study results conducted at their study site shall not be made before the first multicenter publication and as agreed between the sponsor and the Coordinating Clinical Investigator.

For greater certainty, it is hereby recalled that in its capacity as sponsor of the trial, Olympus Europa SE & Co. KG is solely responsible to co-ordinate the publications of multicenter clinical trials in order to ensure that the related results are reported in a coherent and responsible manner so that results from clinical trial data subsets are not published in advance of or without clear reference to the primary publication and/or do not repeat such primary publication. Olympus Europa SE & Co. KG decides about the nomination of investigators as authors on the basis of its internal policies, requirements of the publishers and generally accepted standards of authorship. Therefore, Olympus Europa SE & Co. KG shall be duly informed of any publication plans in order to review any proposed manuscript before submission for publication.

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16 STUDY TIMELINE

Screening period	May/June 2019 – May/June 2020
Recruitment period:	May/June 2019 – May/June 2020
Database lock	July 2020
Data Review Meeting	July 2020
Statistical analysis:	July 2020
First data available	August 2020
Draft report:	November 2020
Final CIR	December 2020

17 ANNEX 01: DEEP ENTEROSCOPY PROCEDURE

17.1 General Information

A lack of frequent stalling of the rotation should be interpretive as a warning to assess the patient and scope position.

Continued rotation without advancement should also be seen as maximum insertion depth.

The limit function does not guarantee the safety of the procedure. The operator must judge if safe insertion can be continued on a case-by-case basis.

The LIMIT Function?

The limit function stops the rotation of the single use PowerSpiral tube when the electric current to the motor on the endoscope a setting value. To release, remove your foot from the pedal on foot switch.

17.2 General Insertion tips

Gentle forward pressure is used when rotation is started as well as throughout the procedure.

Minimal CO_2 insufflation is recommended as small bowel distention will decrease spiral advancement.

Irrigation using a water jet may help with lumen visualization and spiral advancement Intermittent external abdominal compression is often helpful to facilitate engagement and advancement of the spiral segment.

17.3 General Withdrawal tips

Insufflation may be used at will at this time.

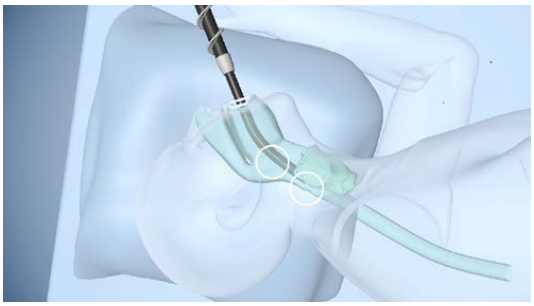
Although the scope may seem to be moving out of the patient quickly, it is important to keep holding the scope firmly.

Slow controlled withdrawal is the key. This is accomplished by backward rotation while maintaining the scope position and keeping the tip in motion

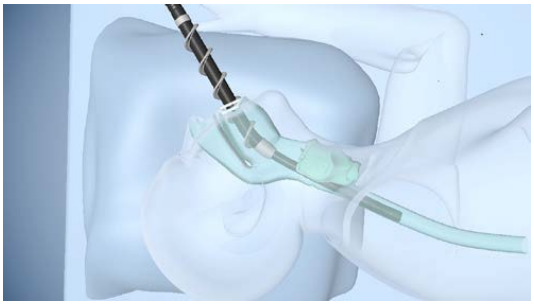
17.4 Antegrade Approach

17.4.1 Inserting the Scope

After passage of the bougie, the tip of the scope is advanced through the mouthpiece into proximal esophagus.



Rotation is started when the spiral segment is in the proximal pharynx. Begin with slow rotation with gentle pressure if needed, and the esophagus is intubated under direct visualization.



Note

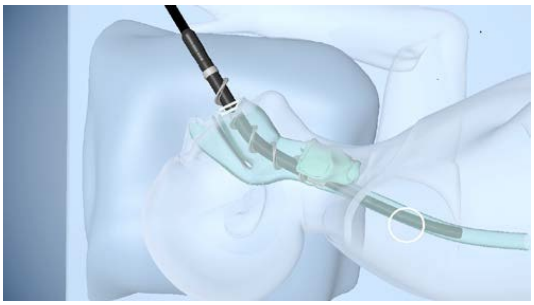
If significant resistance is encountered during esophageal intubation, the endoscope should be removed and the esophagus should be assessed.

If no stricture is observed or motor stalls frequently, consider passage of a large bougie dilator (54-60 Fr) prior to reintroduction of the PowerSpiral.

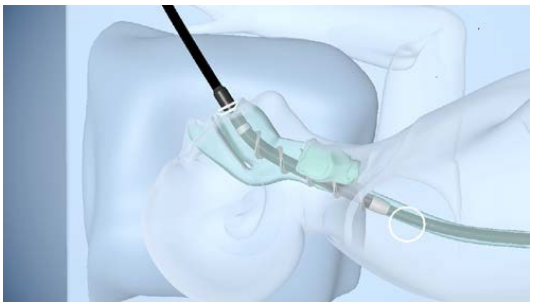
A second attempt may be tried, with deflation of endotracheal balloon considered, but if stalling continues the procedure image is generated is smaller in caliber than the rotary

17.4.2 Passing through the Pharynx & Esophagus

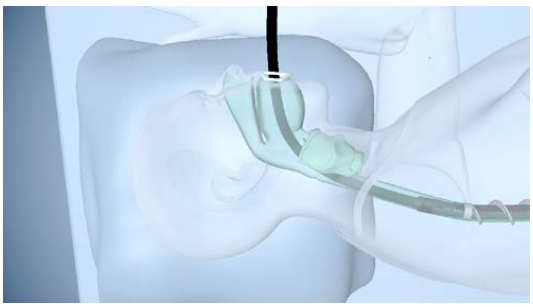
The spiral segment is engaged in the upper esophageal sphincter and rotational advancement is continued using the forward foot switch.



The patient's neck is extended as needed to straighten the passage through the cervical esophagus as the rotating spiral section is less flexible than the remaining section of the scope.



Once the spiral section is past the cervical esophagus, the patient's neck no longer needs to be extended and may be returned to the usual position



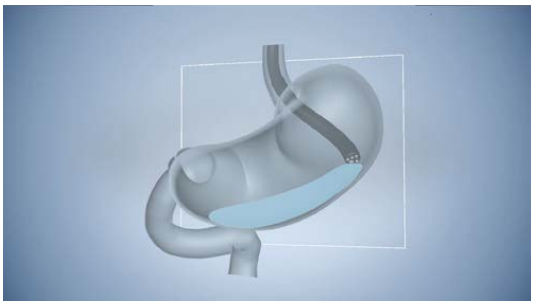
Note

Gentle forward pressure is applied while the spiral segment is rotated slowly and intermittently using the foot switch facilitating intubation of the esophagus.

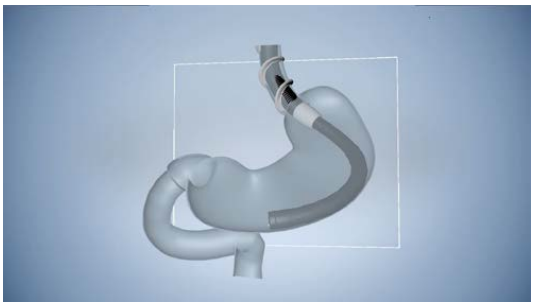
A decrease in the amount of resistance and torque required for advancement is an indicator that the cervical esophagus has been passed.

17.4.3 Passing through the Stomach

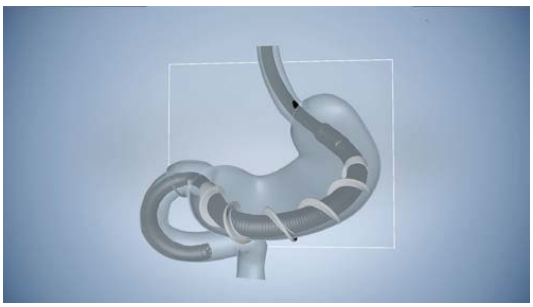
Upon entering the stomach, gastric contents should be aspirated and CO_2 insufflation should be kept to minimum.



While on the stomach, gentle pushing with rotation of the spiral segment is recommended for advancement.

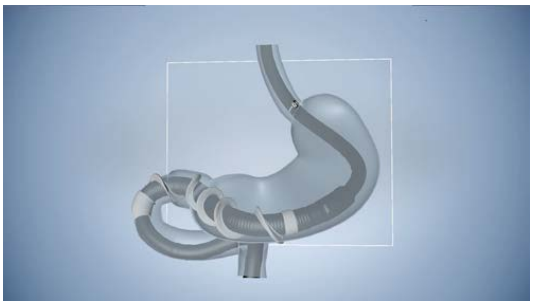


When the insertion tube mark at 80cm is in the mouthpiece, the entire spiral segment is in the stomach.

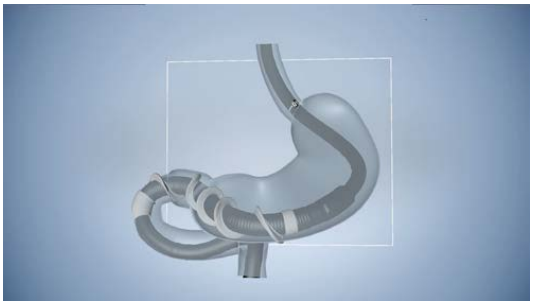


17.4.4 Passing through the Duodenum

The duodenum and proximal jejunum are fixed. Passage through the segment is accomplished with forward rotation and gentle advancement of the scope.



Avoid prolonged rotation when the spiral segment is in the second portion of the duodenum.

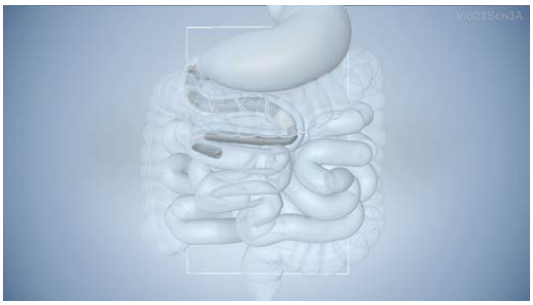


Looping should be avoided but can be managed careful withdrawal of the scope along with forward rotation of the spiral segment.

Fluoroscopy or ScopeGuide may be useful in assessing looping.

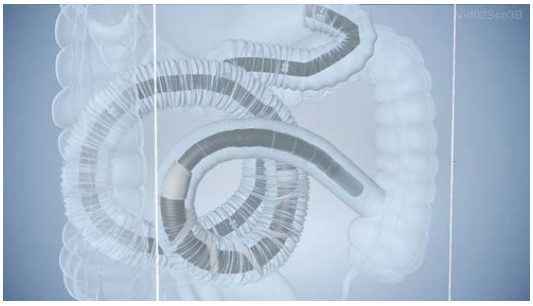
17.4.5 Passing through the Small Bowel Distal to the Ligament of Treitz

Once the spiral segment is positioned in the proximal jejunum, advancement is accomplished primarily by rotation of the spiral segment.



Intermittent gentle advancement of the scope in 3-5cm increments when progress seems to slow down visually.

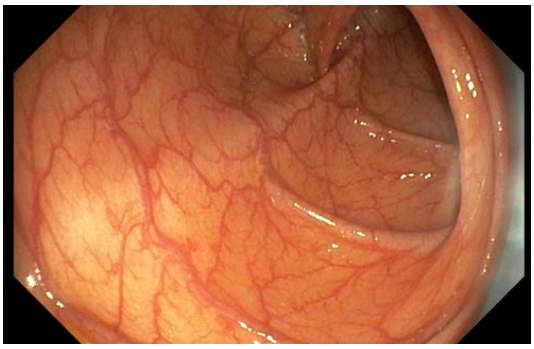
Insert as if drawing concentric circles.



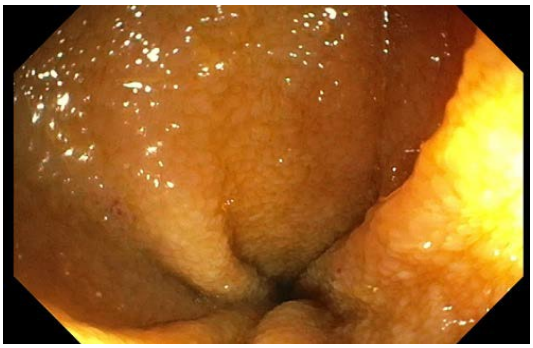
17.4.6 Reaching the Terminal Ileum

The following images will provide indication of the scope being close to the terminal illeum.

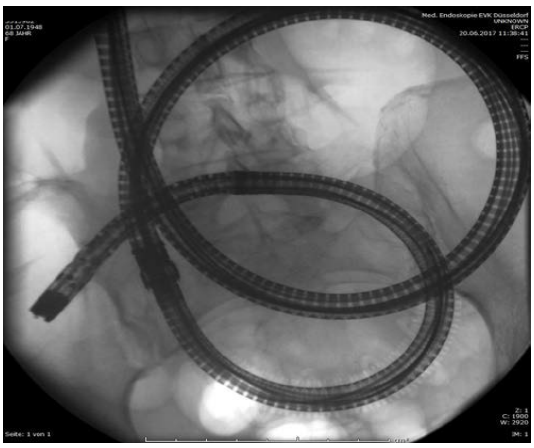
The ileum becomes apparent with less prominent villi and prominent lymphoid follicles.



The procedure should be terminated if the cecum is encountered.

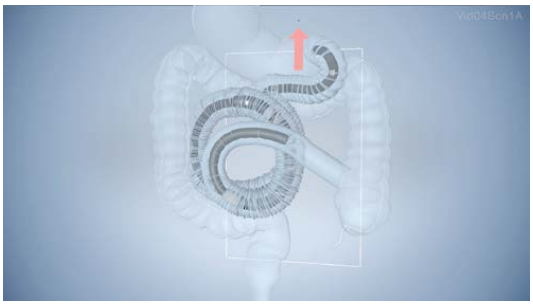


Do not pass the spiral through the ileo-cecal valve. Stop forward advancement.

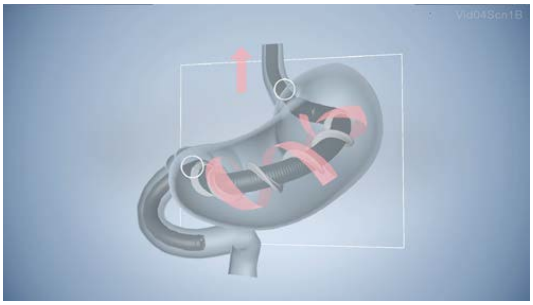


17.4.7 Withdrawal Techniques

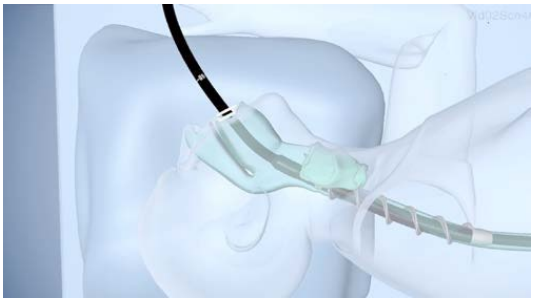
Gentle forward pressure should be maintained to facilitate a slow, controlled withdrawal. This is especially true when the duodenum is encountered.



Every effort should be made to be sure the spiral segment is free in the stomach and no longer engaged in the duodenum/ pylorus prior to allowing the spiral segment to engage the lower esophagus sphincter. This is often accomplished by intermittent use of the forward foot switch to confirm disengagement in the stomach. tent use of the forward foot switch to confirm disengagement in the stomach.



The PowerSpiral enteroscope has a special marking at 80cm to indicate the spiral segment is approaching the lower esophagus sphincter.



As the spiral segment encounters the cervical esophagus, the neck is once again extended to facilitate atraumatic withdrawal while the spiral segment is rotating.

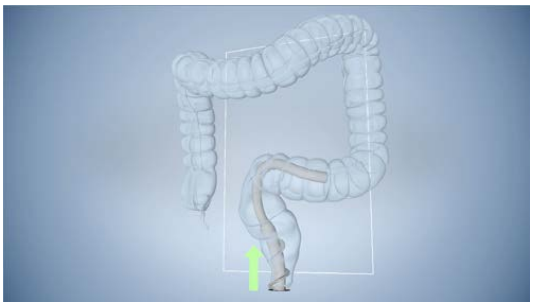
Note

Increased resistance is an indicator of remaining pleated bowel on the spiral segment. This requires advancement of the scope holding position and then resuming backward rotation.

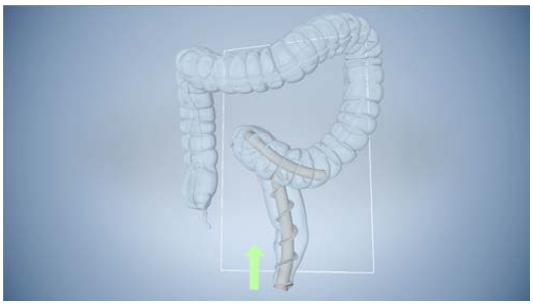
17.5 Retrograde Approach

17.5.1 Passing through the Colon

The spiral enteroscope can be passed through the colon with continuous rotation and gentle pressure.



Forward rotation of the spiral segment should be used for passage through the anal sphincter.



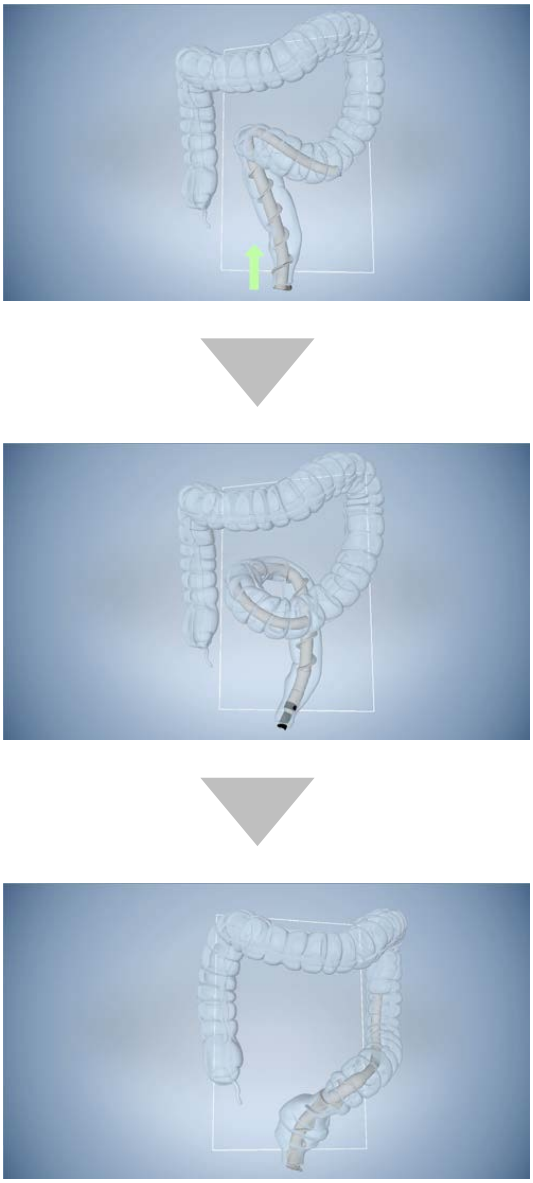
If lumen cannot be visualized, rotate with caution to advance.

CO_2 insufflation should be minimized and water injection should be considered.

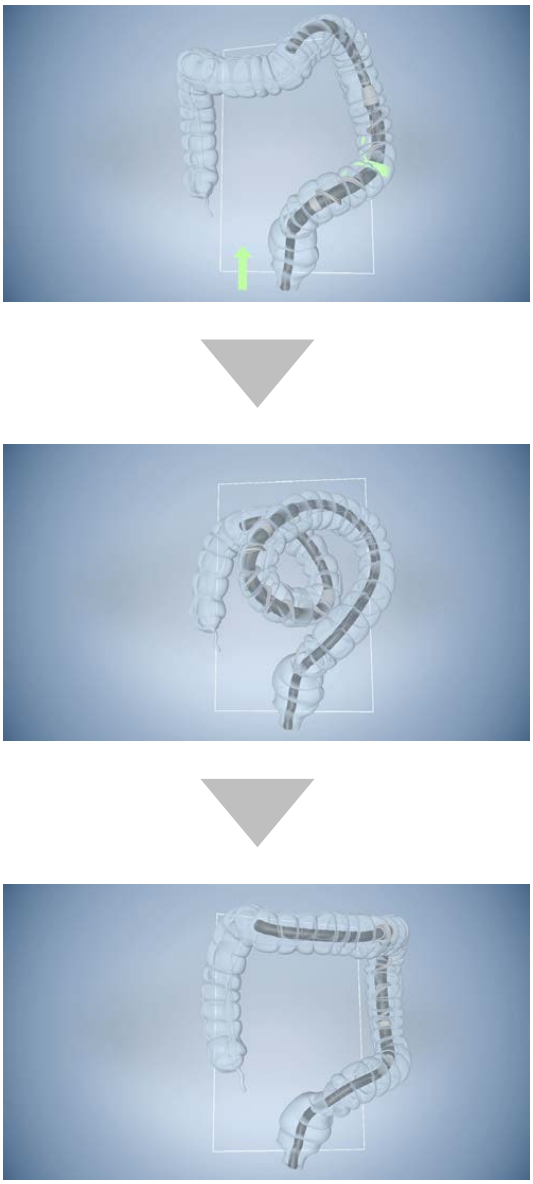
17.5.2 Eliminating a Loop

Eliminate a loop by maintaining position of the spiral segment and withdrawing the scope while applying forward rotation to the spiral segment.

Sigmoid Colon:



Transverse Colon:

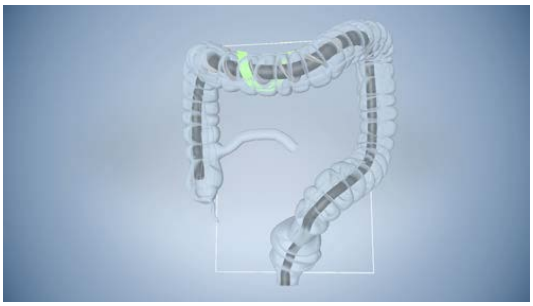


Tips

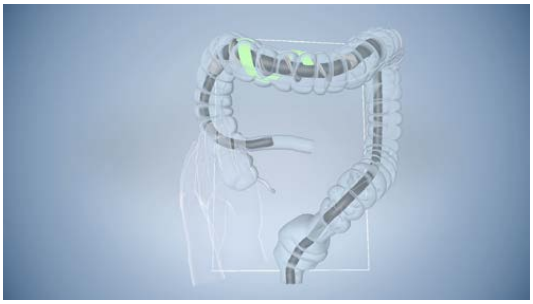
The principal is to minimize the amount of scope inserted in the colon thereby preserving as much scope length as possible with which to examine the small bowel. This is accomplished by minimizing insufflation, and the constant use of withdrawing, torquing, shortening, and pleating techniques.

17.5.3 Passing through the Ileo-cecal Valve

The ileocecal valve is intubated using standard colonoscopy techniques.

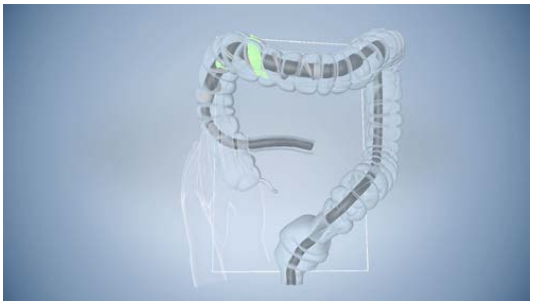


When passing through the ileocecal valve, insertion can be facilitated by decreasing the angle of insertion into the ileum by means of manual compression or postural change.



If insertion into the terminal ileum is still difficult, try retro-flexing the scope inside the cecum and inserting the U-shaped distal end of the scope into the ileum with a push-pull technique.

After passing through the ileocecal valve, advancement is accomplished by rotation of the spiral segment and intermittent advancement of the scope through the rectum as well as intermittent manual compression to facilitate acquisition of the small bowel on to the insertion tube.



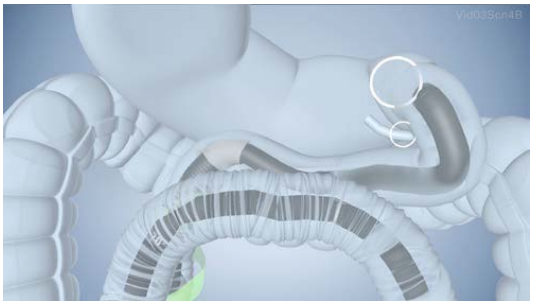
17.5.4 Passing through the Small Bowel

Once the spiral segment is positioned in the terminal ileum, advancement is accomplished primarily by rotation of the spiral segment and intermittent gentle advancement of the scope in 3-5 cm increments when progress seems to slow down visually.

17.5.5 Reaching the Proximal Jejunum

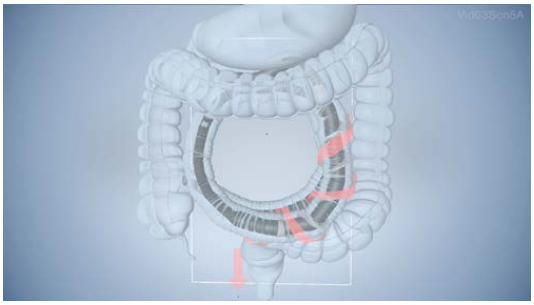
The following images will provide indication of the scope being close to the proximal jejunum.

The procedure should be terminated if the ampulla or duodenal bulb is encountered.

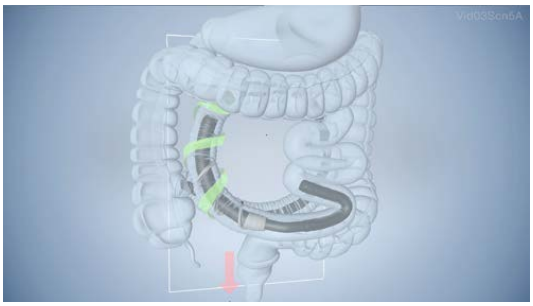


17.5.6 Withdrawal Techniques

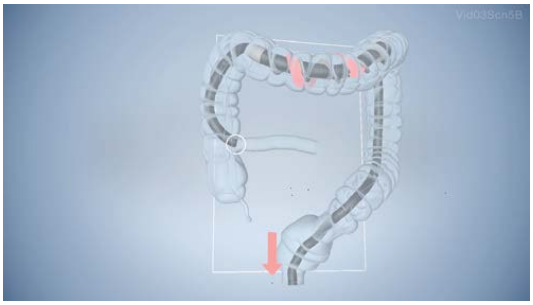
Slow withdrawal is accomplished with the foot switch in the reverse position and constant maneuvering of the scope tip to facilitate gradual and controlled release of the intestine off the tip of the scope.



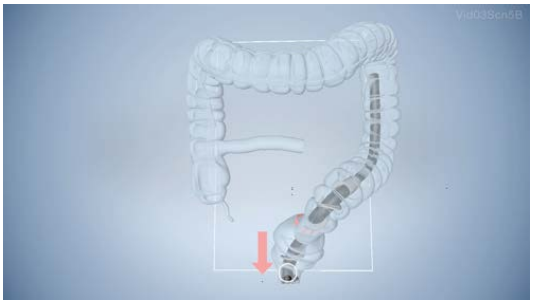
Occasional forward activation of the spiral may be necessary for a slow, controlled withdrawal.



Once the cecum is reached, the scope is withdrawn as in a standardized colonoscopy with or without spiral rotation.



When the anal sphincter is reached, the passage is accomplished by the spiral rotation in the backward direction.



Note

Retroflextion should not be performed with the spiral segment in the patient.