Clinical Study Protocol

Multicenter clinical trial for the evaluation of safety and effectiveness of Endorail in patients with long-lasting colonoscopy

Study acronym	Endorail
Sponsor	Endostart s.r.l., Via delle Regioni 265, 50052 Certaldo (FI), Italy
Investigational Product:	Endorail Set and Endorail System
Protocol Version and Date:	V 1.1, Date: 24 October2022

Sponsor Signature Page(s)

Study Title: Multicenter clinical trial for the evaluation of safety and effectiveness of Endorail in patients with long-lasting colonoscopy

Endostart s.r.l. has approved the protocol version 1.1 dated 24 October 2022

Printed name of Sponsor Representative: Alessandro Tozzi

Date	Signature

Principal Investigator:

I have read and understood this protocol entitled "Multicenter clinical trial for the evaluation of safety and effectiveness of Endorail in patients with long-lasting colonoscopy" and agree to conduct the study as set out in this study protocol, ICH-GCP E6 guidelines or ISO 14155 standard and the local applicable regulations. I will provide all study personnel under my supervision with all information provided by the Sponsor and I will inform them about their responsibilities and obligations.

Site Humanitas Research Institute, Rozzano, Milan, Italy

Principal Investigator Prof. Alessandro Repici, Department Director and Head of Operative Unit of Gastroenterology and Digestive Endoscopy

Date	Signature

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STUDY SYNOPSIS

Sponsor	Endostart s.r.l., Via delle Regioni 265, 50052 Certaldo (FI), Italy
Study Title	Multicenter clinical trial for the evaluation of safety and effectiveness of Endorail in patients with long-lasting colonoscopy
Study Acronym	Endorail
Protocol Version and Date:	V1.1 Date: 24th October 2022
Clinical Phase:	Post-market
Background and Rationale:	This clinical trial is intended to expand the clinical knowledge base about safety and efficacy of Endorail in facilitating colonoscopy completion in patients with long lasting colonoscopy. Reported incomplete colonoscopy rates range from 4% to 25%. While international guidelines recommend a rate of less than 10% for diagnostic colonoscopies, the risk is at least 20% in the more challenging subset of patients characterized by long-lasting procedures. A colonoscopy can be defined as "long-lasting" when caecal intubation time is longer than 10 minutes. As data from literature shows that about 80% of all diagnostic colonoscopies are typically completed in less than 10 minutes, the long-lasting colonoscopy subset represents approx. 20% of the total procedures. Indeed, since nearly virtually all incomplete colonoscopies are also long-lasting, the risk of incompleteness in this subset of patients increases nearly five-fold (i.e., for a 5x increase, the lower bound of the rate increases from 4% to 20%) [1]. Endorail is intended to facilitate the positioning of a standard colonoscope. One of the main advantages of this device is that it can be used "as needed" during the procedure to prevent incomplete procedures without requiring any "preloading" ahead of time. This makes Endorail particularly indicated for patients in which caecal intubation time gets longer and the risk of incompletion increases.

Objective(s):	Primary Objectives: Efficacy (Timeframe: day 1): To validate the efficacy of Endorail in long-lasting colonoscopies by reaching a colonoscopy incompletion rate minor or equal to 10%. AND Safety (Timeframe: day 1 to day 7): To validate the safety of Endorail in long-lasting colonoscopies by demonstrating that colonoscopy serious adverse events are not increased using the device (i.e., in particular the absence of device-related serious adverse events).
Endpoint(s)	Efficacy: The primary efficacy endpoint is the percentage minor or equal to 10% of incomplete long-lasting colonoscopies (colonoscopy is defined completed when caecal intubation is achieved) AND Safety: Medical adverse events and medical device adverse events will be collected during the study. The primary safety endpoints are: The absence of device-related serious adverse events. AND The evaluation of the equality or reduction of the adverse events rates compared to colonoscopies without Endorail. The adverse events assessed are: • Occurrence of general adverse events and medical device incidents; • Occurrence of specific adverse events: gastrointestinal bleedings, intestinal perforation, mucosal petechiae and abdominal pain.
Study design:	Multi Centre, Post Market, Single-Arm, Open-Label, Interventional Study

Inclusion / Exclusion criteria:	Inclusion Criteria 1. Patients of both sexes aged between 22 – 75 years (inclusive); 2. Outpatients undergoing long-lasting diagnostic or surveillance colonoscopy; long-lasting colonoscopy is defined as follows: colonoscopy completion (caecal intubation) not achieved after 10 minutes from endoscope insertion through the anal canal; 3. Patients have given a written informed consent for participation in the study at the time of enrolment or before. 4. Patients able to understand the full nature and the purpose of the investigation, including possible risks and side effects, able to cooperate with the Investigator and to comply with the requirements of the entire investigation based on Investigator's judgement. Exclusion Criteria 1. Body mass index (BMI) > 30 kg/m2; 2. Outpatients undergoing colonoscopy for colorectal cancer screening or therapeutic indication; 3. Patients in class >2 physical status of the classification system of American Society of Anesthesiologists; 4. Any contraindications to colonoscopy; 5. Any contraindications to sedation; 6. Known allergy or hypersensitivity to any of the elements of the Endorail Set (e.g.: iron); 7. Patients with permanently or semi-permanently implanted medical devices, e.g. orthopedic implants, trauma fixation devices, cardiac pacemakers, implantable cardioverter defibrillator, drug pumps, neurostimulators, vascular stents, cochlear implants, aneurysm clip); 8. Presence of dense diverticulosis; 9. Presence of diverticulitis; 10. Presence of ferromagnetic foreign body; 11. Presence of large abdominal hernias; 12. Urgent colonoscopy.

	13. Presence of severe thrombocytopenia; 14. Presence of severe granulocytopenia; 15. Presence of severe coagulopathy; 16. Presence of peritonitis; 17. Presence of colonic wall ischemia or necrosis or injured mucosa;; 18. Presence of peritoneal carcinomatosis; 19. Boston Bowel Preparation Scale <2 in at least one of the colonic segments; 20. Presence of obstructing masses and strictures of the colon; 21. History of total or subtotal colectomy; 22. Presence of angulated and fixed colon curves; 23. Pregnant or breast-feeding women; 24. Patient unable to provide the signed informed consent, uncooperative patient or patient unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study; 25. Presence of any other reason that, in the opinion of the investigator, prevents the subject from participating in the study or compromises the subject safety; 26. Concomitant participation in other clinical investigations or participation in the evaluation of any investigational product/device in the 30 days before this study or previous participation in the same investigation;

Measurements and procedures:	Methodology: Outpatients of both sexes, aged between 22 and 75 years (inclusive), undergoing to diagnostic o surveillance colonoscopy, who have signed a written informed consent and a caecal intubation time greater than 10 minutes (long-lasting colonoscopy), will take part in the study. The study plan will include a screening/baseline/treatment visit (Visit 1/Day 1), during which the colonoscopy will be performed with the investigational medical device Endorail, if long-lasting; AND a phone follow-up visit (Visit 2), scheduled 7 (± 1) day after treatment for patients treated with Endorail. Since only patients with long-lasting colonoscopy will be actually enrolled (i.e., Endorail will be used during the colonoscopy only when the intubation time is longer than 10 minutes), about 80% of patients who signs the informed consent will likely not be enrolled.
Study Product	Endorail Set and Endorail System (Endostart s.r.l., Certaldo, Firenze, Italy) are the investigational medical devices to be used in this study. Endorail is composed of the following two CE marked medical devices: - Endorail Set (including Endorail Balloon Guide, and Endorail Solution Syringe, Endorail Powder and Spike) - Endorail System (including Endorail Handpiece and Endorail Cart).
Sample size calculation:	With a significance level α of 5%, assuming a proportion of outcome of 10.1%, 85 patients allow to test with a power of 80% the H0: $p \geq 20\%$ vs H1: $p < 20\%$, where 20% is the estimated percentage of incomplete procedure from literature. The chosen number is then increased by 10% to account for possible drop-out (e.g., cases to be discarded, losses to follow-up, etc.), resulting in 85/0.90 = 95 patients to be actually enrolled.

Study Duration:	Enrollment period: approximately 8 months; Follow up: 1 week; One single procedure (long-lasting colonoscopy).
Study Schedule:	Month/Year of First-Patient-In (planned): September 2022 Month/Year of Last-Patient-Out (planned): June 2023
Study Centre(s):	Multi-center study: Conducted in Italy, Belgium and Germany.
Statistical Considerations:	A single-arm trial will be carried out to evaluate the safety and the completion rate in long-lasting colonoscopies conducted with Endorail. All data obtained in this study and documented in the eCRFs will be listed and summarized as appropriate: • for quantitative variables: standard quantitative statistics (N, mean, standard deviation, median, interquartile range, minimum and maximum); • for qualitative variables: frequency distribution [number of non-missing observations (N) and percentages (%)]. A statistical test will be performed to assess the significant difference with respect to the threshold. The number of adverse events (AEs) – related or not to the medical device – and the number and proportion of patients with at least one AE will be presented. The frequency of occurrence of specific adverse events (gastrointestinal bleedings, intestinal perforation, mucosal petechiae, abdominal pain) will be presented by means of default descriptive statistics. Analyses will be carried out using R Statistical (Foundation for Statistical Computing, Vienna, Austria).
GCP Statement:	This study will be conducted in compliance with the protocol, the ICH-GCP E6 or ISO 14155 (as far as applicable), 21 CFR 812.28 as well as all applicable regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Event
ASADE	Anticipated Serious Adverse Device Effect
BMI	Body Mass Index
CA	Competent Authority
CEC	Competent Ethics Committee
CFR	Code of Federal Regulations
CIP	Carbonyl Iron Particles
CRF	Case Report Form
eCRF	Electronic Case Report Form
DD	Device Deficiency
DRM	Data Reviewed Meeting
DSUR	Development safety update report
EBG	Endorail Balloon Guide
EC	Endorail Cart
EH	Endorail Handpiece
EP	Endorail Powder
ESS	Endorail Solution Syringe
FDA	Food and Drug Administration
FIM	First In Man
GCP	Good Clinical Practice
GI	Gastro-Intestinal
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
ICD	Implantable Cardioverter Defibrillator
ICE	Integrated Clinical trial Environment
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat

MD	Medical Device
PI	Principal Investigator
PT	Preferred Term
PP	Per- Protocol
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
SDV	Source Data Verification
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

STUDY SCHEDULE

Table 1 – Study Schedule of Assessments

	Screening/Baseline/ Treatment with Endorail System	Phone Follow-up Visit
Visit Day	V1 1	V2 7 ± 1
Informed consent	X	
Demographic data	X	
Medical history	X	
Concomitant treatments	X	X
Physical examination	X	
Vital signs pre-procedure	X	
Inclusion/exclusion criteria	X	
Use of sedation	X	
Colonoscopy with Endorail	X	
Local (intraprocedure) adverse events	X	
Vital signs after procedure	X	
Colonoscopy completion	X	
General/specific adverse events	X	X

1. BACKGROUND AND RATIONALE

1.1 Aim

The aim of this study is to test the safety and efficacy of the Endorail in ensuring low incompletion rate in long-lasting colonoscopies.

1.2 Background and Rationale

1.2.1 Optical colonoscopy

Optical colonoscopy represents the diagnostic and therapeutic gold standard for colonic diseases [23].

1.2.2 Incomplete colonoscopy

A colonoscopy can be defined as incomplete when the endoscopist cannot reach the last segment of the colon called caecum. In particular a colonoscopy is incomplete when the endoscopist feels that it is not useful anymore to continue the procedure and make further efforts [15]. Because neoplasms or other pathologies may occur in any part of the colon, it is essential to complete colonoscopy and also explore the right segments. In case the caecum is not reached, the endoscopist always recommends to complete the examination with a second procedure. The completion is usually performed with virtual colonoscopy or deep sedation colonoscopy possibly with a more experienced endoscopist. However, it was found that about 30% of patients with incomplete colonoscopy after one year from the examination have not carried out any complementary investigation yet. The execution of a complementary examination entails an increase in overall costs for both the health care system and the patient [4]. In fact, the latter will have to carry out the intestinal preparation and undergo further invasive procedure. The cost of the complementary procedure may fluctuate from 250 to 1,000 Euros in relation to the type of procedure [22].

Thus, caecal intubation is one of the main goals of colonoscopy and represents a diagnostic quality indicator. International guidelines recommend caecal intubation rates ≥90% for all colonoscopies in daily clinical practice and ≥95% in screening programs. Reported incomplete colonoscopy rates range from 4% to 25%. Caecal intubation fails in 4-10% of cases in tertiary referred centres), instead in national surveys colonoscopies are incomplete in 10-25% of cases [25][21][27][1].

1.2.3 Long lasting colonoscopy

A colonoscopy can be defined as difficult or long-lasting when caecal intubation time is longer than 10 minutes. Long lasting colonoscopies are cause of stress and delays in the workflow. Moreover, longer procedures are characterized by more traumatic manoeuvres, increased pain and discomfort, higher sedation requirements and higher risk of severe complications such as cardiorespiratory events and bowel perforation.

As data from literature shows that about 80% of all diagnostic colonoscopies are typically completed in less than 10 minutes, the long-lasting colonoscopy subset represents approx. 20% of the total procedures. Indeed, since nearly virtually all incomplete colonoscopies are also long-lasting, the risk of incompleteness in this subset of patients increases nearly five-fold (i.e., for a 5x increase, the lower bound of the rate increases from 4% to 20%) [1][7][17][20].

1.2.4 Complications in colonoscopy

Severe complications such as cardiorespiratory events and bowel perforation, although rare, can develop during colonoscopy [10]. Serious gastrointestinal events; myocardial infarction; stroke; pneumonia occurrence rates in screening or surveillance colonoscopy are 47 persons, 4 persons, 7 persons and 10 persons per 100'000, respectively [30].

1.2.5 Looping

One of the main risk factors for incomplete colonoscopy is colon loop formation [1] Moreover, looping can make colonoscopy a time-consuming procedure requiring manoeuvres that demand a significant amount of training.

The frequency of occurrence of loops during endoscopy is high and may reach proportions of 80-90% of cases of endoscopy [5][12].

Looping is the process where the scope tip does not progress forward when the endoscopist pushes the scope into the patient, but rather the mid-section of the scope bows out, resulting in stretching of the colon. If the endoscope is being inserted into the colon by simply pushing it forward and steering the tip, the shaft pushes against the colonic wall until the colon and its surroundings provide sufficient counter pressure to force the shaft to bend. In practice, this means that the colon is often stretched substantially. This frequently leads to formation of loops in the flexible endoscope shaft and colon, which can hinder further advancement of the tip [32][9]. The functionally necessary flexibility and length of the scope shaft and the floppy nature of the colon and its attachments may prohibit reaching the cecum and visualizing the entire colon [2][8][13][19][24][3][16].

Abdominal pain is mainly due to the traction on the mesenteries exerted by the colonoscope with the intent to solve eventual loops. Moreover, such manoeuvres enhance the risk of colon perforation, discomfort, undue pain and longer recovery time [12]. Sedation is often used to prevent pain. Studies using magnetic endoscopic imaging correlated that looping in the sigmoid colon causes significant pain that can alter colonoscopy outcomes [28]. Most of the forces are exerted on colonic walls whilst the instrument is looping [9]. The colon is rarely perforated by the tip of the colonoscope. Perforations usually occur when the endoscopist is pushing the colonoscope to get around a curvature. The curvature expands more and more as the colonoscope is being pushed in without advancing the tip, and suddenly, the outer wall of the colonoscope splits from the expanding loop [32]

It is important for endoscopists to pay attention to loops and to straighten the instrument by adequate endoscopic techniques such as hooking, torque, jiggling, pull back, and suctioning excess air. However, these techniques are not easy to be managed and demand a significant amount of training [18][1].

1.2.6 Endorail and Looping

The first generation of Endorail has been tested in 2020 in a first in human clinical trial called ESPILOT2019H. This clinical trial provided first clinical data about safety and efficacy of Endorail. In particular this trial showed that Endorail is able to facilitate loop resolution. The current study has been conceived considering that Endorail should allow to facilitate colonoscopy completion. Long-lasting colonoscopies represents a challenging subset of patients with higher risk of incomplete colonoscopy. Our study is intended to demonstrate the efficacy and safety of the Endorail in ensuring that incompletion rate, even in long-lasting colonoscopies, is lower than the

10% threshold as recommended by international guidelines.

1.3 Investigational Product Description

Endorail is a colonoscopy add-on device developed to be used without any modification to colonoscopes and peripheral devices currently utilized. It is an accessory for colonoscopy aimed at facilitating progression of the endoscope in the large intestine. Endorail works as a magnetic anchor that is able to guide the colonoscope and to straighten colon curves and loops.

A second generation of Endorail has been developed and Endorail is composed by the following two CE marked medical devices: Endorail Set and Endorail System.

The reusable **Endorail System** consists of:

- The Endorail Handpiece (EH)
- The Endorail Cart (EC)

The single-use **Endorail Set** consists of:

- The Endorail Balloon Guide (EBG)
- The Endorail Solution Syringe (ESS)
- The Endorail Powder (EP)
- Spike

1.3.1 Endorail Intended Use/Indications for Use

Endorail is composed by the two medical devices Endorail Set and Endorail System.

- Endorail Set is a medical device intended to facilitate the endoscope positioning during colonoscopy. The use of Endorail Set is closely linked to the use of the medical device Endorail System.
- Endorail System is intended to attract and lock in place Endorail Balloon Guide (part of the medical device Endorail Set) inside the colonic lumen, in order to facilitate the endoscope positioning during colonoscopy. The use of Endorail System is closely linked to the use of the medical device Endorail Set.

1.3.2 Principles of Operation and Technological Characteristics

For exhaustive description of the device and its usage see the Endorail Set and Endorail System instructions for use.

Colonoscopy represents the gold standard procedure for colorectal cancer prevention [11]. Its completion maximizes the possibility of detecting tumors in all colonic segments. However, intubation of the cecum may be challenging due to the occurrence of loops in the colon [1]. In these cases, the tip of the scope cannot move forward, the endoscope increases the wide angle of the loop [5] and the patients can suffer intense pain [29]. While the endoscopist may try to straighten the scope, unfortunately this is not always easy or feasible [**Error! Reference source not found.**][1].

In case of long-lasting colonoscopy, the Endorail Balloon Guide can be inserted inside the endoscope tool channel. The balloon guide is connected at its proximal (user) end to the syringe

containing the Ferromagnetic Fluid which is a magnetorheological mixture composed of solid micrometric carbonyl iron powder particles dispersed in a hypertonic water solution of salts (NaCl and Sodium Citrate).

The ferromagnetic fluid syringe needs to be prepared by the nurse according to the following steps:

- the water solution of the ESS is injected in the vial containing the iron powder EP
- the vial is shaken
- the ferromagnetic fluid is aspirated within the syringe
- the syringe filled with ferromagnetic fluid is ready to be connected with the balloon catheter

The balloon is advanced beyond the colonoscope tip and filled with 25 mL of biocompatible Endorail Ferromagnetic Fluid. The operator manually performs and controls the inflation and deflation of the balloon through the syringe. Thus, by applying the Endorail Handpiece over the patient abdomen, the balloon can be magnetically anchored. The magnetic power level can be increased by the operator according to the patient's body mass characteristics and the successful anchorage of the balloon can be visually verified by the operator through the images captured by the colonoscope.

The anchored balloon guide allows to straighten the scope and thus the colon itself. As the balloon guide is kept in tension, its rigidity increases and works as a rail supporting the movements of the colonoscope. The guided colonoscope can thus be easily moved back and forward to allow better colonoscope positioning and colonoscopy completion.

The Endorail Balloon Guide pulled against the colonic wall by the handpiece magnetic field works as a distal anchor towards which the endoscope tip is advanced and the Endorail Balloon Guide inflation tube serves as a guide wire that leads the endoscope as it is pushed towards the magnetically anchored balloon. After the Endorail is removed, the straightened colonoscope can be easily pushed forward to achieve colonoscopy completion as foreseen in standard endoscopic technique.

The Endorail Balloon Guide does not affect the endoscope's flexibility, its field of view and the maneuverability of the endoscope's tip, nor does it limit the use of any standard endoscopy tools such as biopsy forceps, snare, needle etc. The Endorail Balloon Guide can be pulled back at any time during the procedure in order to allow the use of therapy tools.

1.4 Clinical Evidence to Date

With the intent of providing clinical evidence to further support the safety and efficacy profile of the Endorail, a First-In-Man (FIM) clinical trial has been conducted. This study, named "ESPILOT2019H", was initiated on February 11, 2020, and required the enrolment of a total of 25 evaluable Italian patients undergoing elective colonoscopy. Following the enrolment of the first six (6) patients however, the particularly severe COVID-19 outbreak experienced in Italy forced an early interruption of the study recruitment by the affected medical centers. Given the great uncertainty about a realistic timeline for a possible study resumption, Endostart decided to terminate the trial on March 11, 2020. This decision was not due to the occurrence of any adverse events, or safety concerns, or other device-related reasons.

All 6 patients completed the colonoscopy in the expected timeframe without any adverse event or complications. Five (5) of the six (6) enrolled patients completed the study according to the protocol. In the very first patient however, due to an error of the device technical information

sheet, a pediatric colonoscope was utilized with a tool channel diameter smaller than required (3.2 mm instead of 3.7 mm), which did not allow the successful insertion of the Endorail Balloon Guide. For this one patient, the colonoscopy was continued and completed in the traditional manner without the use of the subject device.

Following a protocol amendment, whereby the reference colonoscope channel diameter to be used was specified to be ≥ 3.7 mm, all loops formed in the other 5 patients were successfully resolved with the Endorail.

1.5 Study rationale

By facilitating loop solving, Endorail should be able to provide several potential benefits, which include fewer attempts at straightening the scope, shorter duration of looping, decreased mean caecal intubation time, higher procedure completion rates, higher diagnostic efficiency, reduced health care costs, reduced stretching forces exerted on the colon walls and attachments, reduced risk of perforation during diagnostic colonoscopy, reduced risk of splenic injury during diagnostic colonoscopy, reduction of the evoked pain and patient discomfort, reduction, and in some cases elimination, of the need for sedation, and reduction of cardiorespiratory complications. All these benefits need to be demonstrated in properly designed clinical trials.

The current study has been conceived considering that Endorail should allow to facilitate colonoscopy completion. Long-lasting colonoscopies represents a challenging subset of patients with higher risk of incomplete colonoscopy. Our study is intended to demonstrate the efficacy and safety of the Endorail in ensuring that incompletion rate, even in long-lasting colonoscopies, is lower than the 10% threshold as recommended by international guidelines.

1.6 Explanation for choice of comparator

Caecal intubation rate is an important quality measure in colonoscopy. The completion of the insertion process by fully intubating the cecum allows the endoscopist to perform a complete examination of the colon mucosa upon withdrawal. Caecal intubation is an objective parameter that, according to the standard of care, should be collected during any colonoscopy. International guidelines recommend achieving an incompletion rate lower than 10%. This numerical target value is derived from historical data from clinical studies and may be used as effectiveness endpoint (See Section 1.4).

Adverse events occurrence during colonoscopy is well documented in international literature and can be used as safety endpoint.

Considering the extensive objective data available from literature and the standard of care, we believe that valid scientific evidence to determine whether there is reasonable assurance that the Endorail is safe and effective may come from an objective trial without matched controls.

1.7 Risks / Benefits

Patients with long lasting colonoscopy are characterized by high risk of incomplete colonoscopy and adverse events. Indeed if caecal intubation time is longer than 10 minutes, it means that the procedure is more challenging and traumatic and more sedation is required. Endorail has been developed to facilitate colonoscopy completion, thus it can provide a significant benefit to this population.

From a safety perspective, reassuring evidence supports the safety of magnetic devices for endoscopic procedures. Magnets in gastrointestinal endoscopy are involved in applications such as

magnetic maneuverable capsule endoscopy, magnetic foreign body removal, magnetically tracked enteral tube placement, compression anastomosis, magnetic anchoring, magnetic retraction, magnetic sphincter augmentation and magnetic tumor marking [6].

There have been several reports of anchoring technology in humans. Dominguez et al reported no magnet related complications or conversions using neodymium magnetic forceps in 40 patients undergoing laparoscopic cholecystectomy [10]. The Magnetic Surgical System (by Levita Magnetics) is indicated in the U.S. to grasp and retract the body and the fundus of the gallbladder in laparoscopic cholecystectomy and the liver in bariatric procedures to facilitate access and visualization of the surgical site.

PUMA-G System (by CoapTech LLC) is an accessory to enteral feeding tubes that, using the magnetic anchoring of its balloon, enables ultrasound-based placement of percutaneous gastrostomy feeding tubes. In particular the balloon of the device PUMA-G System is filled with a saline solution and the magnetic anchoring force towards the external magnet is ensured by a small magnetic needle hosted within the balloon.

Endorail magnetic balloon anchorage is exerted thanks to the Endorail Ferromagnetic Fluid which is a dispersion of micrometric carbonyl iron particles (CIP) in hypertonic water-based solution containing sodium citrate and sodium chloride. The ferromagnetic fluid contained in the syringe is not intended to be in contact with the patient, however the possibility of a contact has been taken into account. Carbonyl iron particles incorporate excellent biocompatibility and safety factors with their unique magnetic properties; therefore, they have been used in biomedical applications such as oral iron supplements for iron deficiency anemia.

Evidences gathered in literature suggest that carbonyl iron powders possess a low potential for acute systemic toxicity when ingested. This is most likely related to the long solubilization process that they undergo into the stomach. Since such solubilization process does not take place into the large intestine, it is deemed unlikely for a CIP to be readily absorbed by the tissues of this body structure. In the case of the Endorail, it is suggested to take appropriate countermeasures to ensure that accidentally poured CIP is endoscopically removed as much as possible from the patient's large intestine. Indeed CIP is grey and in case of leakage it is very easy to be detected. The endoscopist can use the colonoscope to wash the lumen and remove the iron powder in few minutes. These countermeasures and the low probability of absorption by the tissues of the large intestine are expected to contribute to a very low biological risk for the patient.

The planned clinical investigation will assess the safety and tolerability of Endorail by collecting general adverse events and specific adverse events, such as gastrointestinal bleedings, intestinal perforation, mucosal petechiae and abdominal pain. Overall, there are no expected or unexpected risks or complications that may emerge from the use of the Endorail in the patient population selected in this investigational protocol. Therefore, it is expected that benefits from the participation in this investigation will outweigh the potential risks.

1.8 Justification of choice of study population

The study population includes outpatients of both sexes, aged between 22 and 75 years (inclusive), undergoing diagnostic and surveillance colonoscopy, who have signed a written informed consent.

The choice of study population is guided by the need to obtain a homogeneous patients' sample and to collect data that are comparable with those available in the literature, allowing an accurate and unbiased statistical analysis. Moreover, all those conditions that could impair the patient's safety have been excluded.

A population between 22 and 75 years of age has been chosen since the aim is to study the Endorail device in the treatment of adult population; to be compliant with FDA regulation, the age of majority in the United States was used as reference. Moreover, since it is known in the literature that the occurrence of adverse events is greater in the older population, patients aged >75 years are excluded.

Targeting a homogeneous population, the choice to include surveillance and diagnostic colonoscopies is justified by the fact that both refer to comparable guidelines and that the data in the literature are comparable. On the contrary, screening colonoscopies were excluded because they present a different completion rate than the previous two, while therapeutic colonoscopies present a higher risk of occurrence of adverse events.

In conclusion, the population was chosen homogeneously in order to compare it with the data available in literature, to create as few confounding factors as possible and to exclude any conditions that might impact on patient and device safety.

2. STUDY OBJECTIVES

The aim of this study is to test the safety and efficacy of Endorail in ensuring low incompletion rate in long-lasting colonoscopies.

2.1 Primary Objective

Efficacy (Timeframe: day 1)

To validate the efficacy of Endorail in long-lasting colonoscopies by reaching a colonoscopy incompletion rate minor or equal to 10%.

AND

Safety (Timeframe: day 1 to day 7)

To validate the safety of Endorail in long-lasting, colonoscopies by demonstrating that colonoscopy serious adverse events are not increased using the device (i.e., in particular the absence of device-related serious adverse events).

3. STUDY ENDPOINTS

3.1 Primary Endpoints:

Efficacy:

The primary efficacy endpoint is the percentage minor or equal to 10% of incomplete long-lasting colonoscopies (colonoscopy is defined completed when caecal intubation is achieved)

AND

Safety:

Medical adverse events and medical device adverse events will be collected during the study.

The primary safety endpoints are:

The absence of device-related serious adverse events.

AND

The evaluation of the equality or reduction of the adverse events rates compared to diagnostic colonoscopies without Endorail.

The adverse events assessed are:

- Occurrence of general adverse events and medical device incidents;
- Occurrence of specific adverse events: gastrointestinal bleedings, intestinal perforation, mucosal petechiae and abdominal pain.

4. STUDY DESIGN

4.1 General study design and justification of design

The study will be conducted according to a Multi Centre, Post Market, Single-Arm, Open-Label, Interventional Study design, which is considered as the most appropriate for the collection of the clinical data about the safety and efficacy of the Endorail device in completing long-lasting diagnostic colonoscopy or surveillance colonoscopy. Considering that completion rate and adverse events occurrence are widely described in historical data from clinical studies and/or registries and may be used as objective for safety or effectiveness endpoints, the single-arm design can be considered sufficient for the aim of the study.

Outpatients of either sex aged between 22-75 years (inclusive), undergoing elective colonoscopy for diagnostic or surveillance colonoscopy, who have signed a written informed consent and presenting caecal intubation time greater than 10 minutes, will take part in the study. The study plan will include a screening/baseline/treatment visit (Visit 1/Day 1), during which colonoscopy with the investigational medical device Endorail will be performed and a phone follow-up visit (Visit 2), scheduled at 7 (± 1) day after treatment with the investigational medical device Endorail.

4.2 Methods of minimizing bias

The following measures have been implemented in order to minimize avoid/bias:

- New technology bias is minimized through an adequate and thorough training to the endoscopist;
- Low statistical bias is minimized through an adequate estimate of the number of patients in the treatment group as compared to the state of the art;
- Multicentric study to minimize usability bias.

4.3 Eligibility criteria

Inclusion Criteria

1. Patients of both sexes aged between 22 – 75 years (inclusive);
2. Outpatients undergoing long-lasting diagnostic and surveillance colonoscopy; long-lasting colonoscopy is defined as follows: colonoscopy completion (caecal intubation) not achieved after 10 minutes from endoscope insertion through the anal canal;
3. Patients have given a written informed consent for participation in the study at the time of enrolment or before;
4. Patients able to understand the full nature and the purpose of the investigation, including possible risks and side effects, able to cooperate with the Investigator and to comply with the requirements of the entire investigation based on Investigator's judgement.

Exclusion Criteria

1. Body mass index (BMI) > 30 kg/m^2;
2. Outpatients undergoing colonoscopy for colorectal cancer screening or therapeutic indication;
3. Patients in class >2 physical status of the classification system of American Society of Anaesthesiologists;
4. Any contraindications to colonoscopy;
5. Any contraindications to sedation;
6. Known allergy or hypersensitivity to any of the elements of the Endorail Set (e.g.: iron);
7. Patients with permanently or semi-permanently implanted medical devices, (e.g. orthopedic implants, trauma fixation devices, cardiac pacemakers, implantable cardioverter defibrillator, drug pumps, neurostimulators, vascular stents, cochlear implants, aneurysm clip);
8. Presence of dense diverticulosis
9. Presence of diverticulitis
10. Presence of ferromagnetic foreign body;
11. Presence of large abdominal hernias;
12. Urgent colonoscopy;
13. Presence of severe thrombocytopenia;
14. Presence of severe granulocytopenia;
15. Presence of severe coagulopathy;
16. Presence of peritonitis;
17. Presence of colonic wall ischemia or necrosis or injured mucosa; ;
18. Presence of peritoneal carcinomatosis;
19. Boston Bowel Preparation Scale <2 in at least one of the colonic segments;
20. Presence of obstructing masses and strictures of the colon;
21. History of total or subtotal colectomy.
22. Presence of angulated and fixed colon curves;
23. Pregnant or breast-feeding women;
24. Patient unable to provide the signed informed consent, uncooperative patient or patient unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study;
25. Presence of any other reason that, in the opinion of the investigator, prevents the subject from participating in the study or compromises the subject safety
26. Concomitant participation in other clinical investigations or participation in the evaluation of any investigational product/device in the 30 days before this study or previous participation in the same investigation;
27. Urgent colonoscopy.

4.4 Recruitment and screening

Before starting the recruitment, each investigator must be familiar with the device under investigation.

If the Investigator has never used the Endorail device, he/she should perform at least three colonoscopy procedures with Endorail. To assess the performance case, the Investigator should sign a self-declaration titled " Performance case declaration" stating that the three cases have been duly performed in compliance with Protocol requirement.

Before any screening procedure all patients must sign a written informed consent for the study. The following logs must be maintained at each study site and kept in the Investigator Site File: a "Subject Screening Log\Enrolment Log", to document the identification of subjects who enter screening and to document chronological enrolment of patients, a "Subject Identification List" for all subjects registered to maintain the correlation with the patient's full identification data (name, surname - confidential).

Eligible patients who have provided written informed consent to study participation and that satisfy all inclusion criteria and none of the exclusion criteria both detailed in Section 4.3, will be enrolled in the clinical study.

Eligibility will be determined by the investigator basing on standard colonoscopy clinical history and colonoscopy indication. Enrolment will be completed during colonoscopy if caecal intubation time is longer than 10 min.

When the investigator registers in the eCRF the enrolment of a new patient, the eCRF will assign a 4-digit identification number to each patient included in the investigation. The patient number will be sequentially assigned to each patient who signs the informed consent, starting from 0001 . If a subject discontinues from the study, the patient number will not be re-used, and the subject will not be allowed to re-enter the study. Moreover, to distinguish the patient number of different sites involved in the clinical trial, the 4 digit patient number will be preceded by a 2-digit site number. Before the study initiation, the Sponsor will assign to each participating site its unique 2-digit site number.

4.5 Criteria for withdrawal / discontinuation of participants

Patients have the right to withdraw from the investigation at any time for any reason including personal reasons (consent withdrawal). The Investigator also has the right to withdraw any patient from the investigation if he/she deems this appropriate and in the best interest of the patients.

Possible reasons to discontinue a patient from the study include:

- Patients' withdrawal of consent for study participation;
- Adverse events (AEs): occurrence of unexpected symptoms during the study, whose intensity or specific treatments require the discontinuation of the colonoscopy with the investigational product. The reason of discontinuation must be recorded in the medical records and in the eCRF. If necessary, patients will be given an appropriate symptomatic treatment that will be recorded in the medical records and in the eCRF, together with the outcome and the duration of the AE. In case of serious adverse reactions to the investigational device, the study sponsor must be advised within 24 hours and all procedures for the reporting of serious adverse events (SAEs) will be made effective;

- Protocol violation: at least one of the conditions that represent any of the exclusion criteria (refer to Section 4.3). The reason of discontinuation must be recorded in the medical records and in the eCRF;
- The Investigator considers the study procedure discontinuation as appropriate, in the best interest of the patient;
- The Sponsor will terminate the study for any reason (refer to Section 4.6);
- Patient dies during the study: the reason and the date of death will have to be recorded in the medical records and in the eCRF, together with the Investigator's opinion on the correlation between the cause of death and the investigational product.

Should a patient decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the withdrawal (study end-point) should be performed, and a clear, univocal explanation of the reason why the subject is withdrawn from the study should be reported in the medical record.

4.6 Premature Stopping of the Trial

Both the Sponsor and the Principal Investigator reserve this right to terminate the investigation at any time. The Sponsor has the right to terminate the participation of the participant site at any time, for any reason, including but not limited to the following:

- The information on the investigational products leads to doubt as to the benefit/risk ratio;
- Patient enrolment is unsatisfactory and the patient recruitment lags behind the prospected timetable by more than 50%;
- The Principal Investigator has received from the Sponsor all investigational medical products, means and information necessary to perform the clinical study and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Principal Investigator or Sub-investigators, delegated staff with any provision of the clinical study protocol, and breach of the applicable good clinical practice (GCP) requirements. In any case the Sponsor will notify the Principal Investigator of its decision by written notice.
- In particular, when 38 patients (40% of the sample size) and 57 patients (60% of the sample size) are reached, the significance will be tested. If significance is found, the trial can be terminated with the patients already collected.

4.7 Replacements

Patients who withdraw the informed consent before the completion of the procedure can be replaced by newly recruited patients. Similarly, for patients who are found to be lost to follow-up following the procedure completion and therefore cannot be reached by phone for the scheduled follow-up visit (Visit 2) a second and third attempt should be made after the second and third week; if the patient is still untraceable it can also be replaced by newly recruited patients (See section 5.5).

5. STUDY INTERVENTION

5.1 Identity of Investigational Products (medical device)

Endorail (Endostart s.r.l., Certaldo, Firenze, Italy) is the investigational medical device used in this study. For an extensive description of the device, please see the instruction for use.

The Endorail is composed by the following two CE marked medical devices:

- The reusable Endorail System, which consists of:
  - The Endorail Handpiece (EH)
  - The Endorail Cart (EC)
- The single-use Endorail Set, which consists of:
  - The Endorail Balloon Guide (EBG)
  - The Endorail Solution Syringe (ESS)
  - The Endorail Powder (EP)
  - Spike

Endorail Balloon Guide (EBG)

EBG is an on-demand disposable balloon catheter that can be inserted through the instrument channel of the colonoscope. EBG includes the balloon and the inflation tube. The balloon is elastic and is placed at the distal end of the catheter and its maximal capacity is 25 mL. The user may operate and control the inflation and deflation of the balloon through the syringe containing Endorail Ferromagnetic fluid connected at the proximal end of the catheter.

The balloon can be advanced ahead of the endoscope tip or pulled back through pushing/pulling action on the inflation tube at its proximal side, outside the patient's body. The EBG can be pulled back at any time during the procedure in order to allow the use of other endoscopic accessories.

Endorail Solution Syringe (ESS)

ESS included in the Endorail Set is disposable and intended for-single use. The syringe is prefilled with a hypertonic water-based saline solution with high sodium citrate and sodium chloride concentrations.

Endorail Powder (EP)

Endorail Powder is a 50 mL vial containing dry carbonyl iron powder.

Spike

The spike is a tool required for piercing the vial and inject the saline solution in the vial.

Endorail Ferromagnetic Fluid Syringe (EFFS)

Before using Endorail the saline solution contained in the syringe need to be mixed with the iron powder. For this purpose, the ESS is connected with the spike and the spike is connected with EP. After that the saline solution has been mixed with the iron powder, at the end of the preparation phase, the syringe is filled with a water dispersion of iron micrometric particles called Endorail

Ferromagnetic Fluid.

Endorail Handpiece (EH)

Endorail handpiece (EH) contains a powerful permanent magnet. The handpiece is reusable and allows both the safe use of the magnet and the regulation of the magnetic field exerted on the filled balloon. EH is used during the procedure to magnetically anchor the balloon filled with ferromagnetic fluid.

Thanks to a screw-like mechanism the magnet can be moved inside the handle. There are 5 different magnet positions that correspond to 5 different levels of magnetic field intensity. The first level is the weakest and is called MIN Level. The fifth level is the most powerful one and also the most dangerous. For safety reasons EH should be always used and stored carefully following the instruction for use. EH misuse can cause severe adverse events both for patients and users. The magnetic field can interfere with other ferromagnetic objects or electronic devices.

Endorail Cart (EC)

Endorail Cart is used for the storage and transportation of Endorail Handpiece. It is composed by a case and a base with wheels. The case is provided with a shield for magnetic fields to avoid accidental interferences between the magnet and other ferromagnetic objects or electronic devices.

5.2 Experimental Intervention (treatment/medical device)

Endorail is a colonoscopy add-on device developed to be used without any modification to colonoscopes. Endorail is an accessory to an endoscope and is intended to facilitate positioning of a standard colonoscope during endoscopy of the large intestine. Endorail works as a magnetic anchor that is able to guide the colonoscope and to straighten colon curves and loops.

In case caecal intubation time is longer than 10 minutes, the balloon is inserted in the endoscope tool channel, advanced beyond the colonoscope tip and filled with 25 mL of biocompatible Endorail Ferromagnetic Fluid. The operator manually performs and controls the inflation and deflation of the balloon through the syringe. Thus, by applying the Endorail Handpiece over the patient abdomen, the balloon can be magnetically anchored. The magnetic power level can be increased by the operator according to the patient's body mass index and the successful anchorage of the balloon can be visually verified by the operator through the endoscopic images.

For achieving the optimal effectiveness, anchorage should be performed in any colon segments proximal to the sigmoid colon (descending colon, transverse colon, ascending colon, caecum and colon curves).

The anchored balloon guide allows to straighten the scope and thus the colon itself. As the balloon guide is kept in tension, its rigidity increases and works as a rail supporting the movements of the colonoscope. The guided colonoscope can thus be easily moved back and forward to allow better colonoscope positioning and colonoscopy completion.

The Endorail Balloon Guide pulled against the colonic wall by the handpiece magnetic field works as a distal anchor towards which the endoscope tip is advanced and the Endorail Balloon Guide inflation tube serves as a guide wire that leads the endoscope as it is pushed towards the magnetically anchored balloon. After the Endorail is removed, the straightened colonoscope can be easily pushed forward to achieve colonoscopy completion as foreseen in standard endoscopic technique.

The Endorail Balloon Guide does not affect the endoscope's flexibility, its field of view and the manoeuvrability of the endoscope's tip, nor does it limit the use of any standard endoscopy tools such as biopsy forceps, snare, needle etc. The Endorail Balloon Guide can be pulled back at any time during the procedure in order to allow the use of other endoscopic accessories.

EBG is a disposable device however it can be used up to three times in the same patient. For detailed description of the procedure, see the instruction for use of Endorail Set and Endorail System.

5.2.1 Treatment with the investigational device

Each procedure is performed by an experienced endoscopist. If possible, the entire procedure will be video recorded. Sedation will be performed by an anaesthesiologist or an endoscopist according to standard of care.

A standard colonoscope with instrument channel diameter bigger or equal than 3.7 mm will be used for colonoscopy.

Endorail will be used only in case caecal intubation time is longer than 10 minutes. For detailed description of the device and the procedure, see the instruction for use.

5.2.2 Control Intervention (Clinical Practice)

This clinical trial has no prospective control group; results about primary endpoints for efficacy and safety will be compared with the standard clinical practice and international guidelines reference values (Section 1.6).

5.2.3 Packaging, Labelling and Supply

The investigational medical device Endorail Set and Endorail System are produced and packaged by Endostart s.r.l., Via delle Regioni 265, 50052 Certaldo (FI), Italy. Endostart s.r.l. will also supply the investigational medical devices to the investigational study sites.

The labelling of the investigational device Endorail will be performed by Endostart s.r.l. in accordance with the ISO 14155 guideline for medical devices and to all the local requirements.

5.2.4 Handling

The Principal Investigator will be responsible for the correct storage and use of the investigational medical devices, as well as of its accountability (usage and returning). The site staff can be delegated by the Principal Investigator to the abovementioned activities.

The Sponsor of the study will be responsible for the distribution of the investigational medical devices to the site involved in the investigation.

At the end of the investigation, the unused investigational medical devices will be returned to the Sponsor for reconciliation.

5.2.5 Storage Conditions

No specific storage conditions are required for the use of the investigational medical device Endorail, which should be stored at room temperature.

5.3 Administration of experimental and control interventions

5.3.1 Experimental Intervention

Endorail is a colonoscopy add-on device developed to be used without any modification to colonoscopes. Endorail is an accessory to an endoscope and is intended to facilitate positioning of a standard colonoscope during endoscopy of the large intestine. Endorail works as a magnetic anchor that is able to guide the colonoscope and to straighten colon curves and loops.

The procedure can be summarised according to the following description.

In case caecal intubation time is longer than 10 minutes, the balloon is inserted in the endoscope tool channel, advanced beyond the colonoscope tip and filled with 25 mL of biocompatible Endorail Ferromagnetic Fluid. The operator manually performs and controls the inflation and deflation of the balloon through the syringe. Thus, by applying the Endorail Handpiece over the patient abdomen, the balloon can be magnetically anchored. The magnetic power level can be increased by the operator according to the patient's body mass index and the successful anchorage of the balloon can be visually verified by the operator through the endoscopic images.

For achieving the optimal effectiveness, anchorage should be performed in any colon segments proximal to the sigmoid colon (descending colon, transverse colon, ascending colon, caecum and colon curves).

The anchored balloon guide allows to straighten the scope and thus the colon itself. As the balloon guide is kept in tension, its rigidity increases and works as a rail supporting the movements of the colonoscope. The guided colonoscope can thus be easily moved back and forward to allow better colonoscope positioning and colonoscopy completion.

The Endorail Balloon Guide pulled against the colonic wall by the handpiece magnetic field works as a distal anchor towards which the endoscope tip is advanced and the Endorail Balloon Guide inflation tube serves as a guide wire that leads the endoscope as it is pushed towards the magnetically anchored balloon. After the Endorail is removed, the straightened colonoscope can be easily pushed forward to achieve colonoscopy completion as foreseen in standard endoscopic technique.

The Endorail Balloon Guide does not affect the endoscope's flexibility, its field of view and the manoeuvrability of the endoscope's tip, nor does it limit the use of any standard endoscopy tools such as biopsy forceps, snare, needle etc. The Endorail Balloon Guide can be pulled back at any time during the procedure in order to allow the use of other endoscopic accessories.

EBG is a disposable device however it can be used up to three times in the same patient. For detailed description of the procedure, see the instruction for use of Endorail Set and Endorail System.

5.3.2 Compliance with study intervention

Each enrolled patient will be contacted by telephone (V2, see Section 6.2.2) 7 days after the procedure to evaluate the occurrence of general and specific adverse events from the previous visit. To improve the adherence to the follow up, the investigator will recommend the commitment of each participant in concluding the study schedule.
In case the patient does not respond at the scheduled phone visit, a second attempt should be tried one week after V2 and, in case he/she is still untraceable, he/she will be re-contacted two weeks

after V2. In case the contact is still unsuccessful, the patient will be defined as lost to follow up as indicated in Section 5.5.

5.4 Data Collection and Follow-up for withdrawn participants

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for the efficacy and safety of the patient following Endorail procedure up to 7 days after the discontinuation, except in the case of participant death.
If a patient decides to withdraw the informed consent, this process will happen through a specific communication from the patient to the medical doctor; the physician will report the patient decision in the medical record. If the patient decides to withdraw before the procedure completion, no other data will be collected. If the patient decides to withdraw after the procedure, only the safety and efficacy information will be collected to evaluate the safety of the patient following Endorail procedure, up to 7 days after the colonoscopy.

Upon withdrawal of consent, the patient can:

- request that his/her previously collected data are deleted

OR

- accept the retention of the data collected up to the moment of withdrawal.

Since the withdrawal of consent is communicated to the investigator, it will be the investigator who will register the withdrawal in eCRF specifying whether to delete or not all the previously collected data. Moreover, as far as possible, the Investigator will complete the End of Study Visit eCRF page. The Investigator should try to ascertain the reason(s) for withdrawal while fully respecting the patient's rights.

5.5 Lost to Follow-up

A participant will be considered lost to follow-up if the study site is unable to contact him/her. In case of missed phone contact, the investigator or designee must make every effort to reach the participant (i.e., three phone calls). Should the participant continue to be unreachable up to 14 days after the scheduled phone follow-up visit (V2), after at least three contact attempts, he/she will be considered to have withdrawn from the study.

5.6 Trial specific preventive measures

No specific preventive measures other than those indicated in the exclusion criteria (Section 4.3) are foreseen.

5.7 Concomitant Interventions (treatments)

5.7.1 Permitted Medicines

Participants will be allowed to use any concomitant medication necessary for the treatment of pre-existing concomitant pathologies or for intercurrent diseases, provided that they do not interfere with the parameters under investigation.

As anticipated in Section 5.2.1, sedation will be performed by an anaesthesiologist or an endoscopist according to standard of care.

5.7.2 Prohibited Medicines

No prohibited concomitant treatments are currently defined.

5.7.3 Other Interventions

The patient preparation to colonoscopy will be performed according to standard practice used in the investigational study site.

5.7.3.1 Special Precautions

Not applicable. No special precautions other than those detailed in Section 5.2 will be implemented.

5.7.3.2 Management of Specific Adverse Events or Adverse Medical Device Reactions

Specific adverse events will include gastrointestinal bleedings, mucosal petechiae, intestinal perforation and abdominal pain. However, these specific adverse events are general potential adverse events that might occur during colonoscopy. No specific adverse events (AEs) or adverse device effects (ADEs) are described with the use of the investigational product due to the low risks associated with the medical device under study.

5.7.3.3 Medical Care of Subjects after End of Trial

No specific requirements for medical care of subjects after the end of the trial will be implemented.

5.8 Medical Device Accountability

After receipt of the investigational products supplies, the Principal Investigator or his deputy will conduct an inventory and subsequently fill-in and sign the investigational product Delivery Form called "Device Accountability Log". The Principal Investigator or his deputy, will keep an investigational product inventory and accountability records.

The Principal Investigator will keep the investigational products in a locked and secure storage facility, accessible only to those individuals authorised by the Principal Investigator himself.

5.9 Return or Destruction of Medical Device

At the conclusion of the study, a final investigational product inventory will be performed, and the unused investigational products will be returned to the Sponsor together with an investigational product Return Form accurately filled-in and signed by the Principal Investigator or his deputy. If any supplies are missing, this must be specified within the Return Form together with an explanation for the discrepancy.

6. STUDY ASSESSMENTS

6.1 Assessments of Endpoints

The primary endpoint is the evaluation of the efficacy and safety of Endorail in patients undergoing long-lasting colonoscopies.

6.1.1 Assessment of primary Endpoints

The efficacy endpoint is measured at V1 as the successful completion of the long-lasting colonoscopy (Colonoscopy completion is defined as the caecal intubation).

The safety endpoint is evaluated throughout the entire study duration by collecting the medical adverse events and the medical device adverse events.

Adverse events

Definitions, coding, methods of collection of adverse events and medical device incidents are described in detail in Section 7.1.1. Special attention will be given to the following specific adverse events: gastrointestinal bleedings, intestinal perforation, mucosal petechiae and abdominal pain.

Vital signs

The following vital signs will be assessed before and after the procedure (Section 5.2):

- Blood pressure and heart rate will be measured before the procedure;
- Blood pressure and heart rate will be measured at approximately 30 minutes after completing the procedure.

6.1.2 Assessments in participants who prematurely stop the study

Considering the brevity of the follow up period, at the moment of the withdrawn communication the patient will be asked for safety information about the concomitant treatments and the occurrence of any adverse event.

6.2 Procedures at each visit

The study plan scheduled examinations and procedures are summarised in Table 1. The study plan will include a screening/ treatment visit (Visit 1 - Day 1), during which the colonoscopy with the investigational medical device Endorail will be performed. A phone follow-up visit (Visit 2) will be scheduled 7 (± 1) days after treatment with the investigational medical device Endorail.

6.2.1 Treatment Visit - Visit 1 (Day 1)

Potential participant patients, prospectively attending the investigational study to undergo colonoscopy, will be informed, orally and in writing, about the scope of the study, the relevant procedures, the nature of the risks related to the study, and they will be asked to sign and date the written Informed Consent Form.

After the correct obtaining of the Informed Consent, the following assessments and procedures will be performed during Visit 1 (Day 1):

- Demographic data (age, sex, race) will be recorded;
- A detailed medical history, with special attention to previous history of diverticular disease, hysterectomy, gastrointestinal surgery, implantable devices will be recorded in the patient's medical record and in the appropriate section of the eCRF;
- All concomitant medications being taken by the patient, including treatments administered in the last 4 weeks, will be checked and will be recorded in the patient's medical records and in the appropriate section of the eCRF;
- A general physical examination will be performed. The physical examination will include an examination of head, ears, eyes, nose, mouth, skin, heart, and lung examinations, lymph nodes, genitourinary, gastrointestinal, skeletal, and neurological systems. Any identified abnormality should be recorded in the patient's medical records and in the eCRF;
- Height, weight, BMI;
- Vital signs (blood pressure, heart rate) will be measured and will be recorded both in the patient's medical record and in the appropriate section of the eCRF;
- Inclusion/exclusion criteria will be reviewed and eligible patients will be included in the study;
- Pre-procedure sedation will be performed according to the standard of care;
- Procedure for colonoscopy will be started;
- Caecal intubation time will be recorded;
- Colonoscopy will be performed and completed according to procedures detailed in Section 5.2.;
- In case caecal intubation time is longer than 10 minutes, the patients can be enrolled.
- The occurrence of local (intra-procedure) adverse events (i.e. gastrointestinal bleeding, intestinal perforation, presence of mucosal petechiae and abdominal pain) will be checked and (if any) will be recorded in the patient's medical records and in the appropriate section of the eCRF;
- At the end of the colonoscopy, successful or failed caecal intubation will be recorded in the patient's medical record and in the appropriate section of the eCRF;
- Vital signs (blood pressure and heart rate,) will be measured approximately 30 minutes after completing the procedure and will be recorded in the patient's medical record and in the appropriate section of the eCRF;
- The occurrence of general and specific adverse events from obtainment of Informed Consent Form will be checked and (if any) will be recorded in the patient's medical records and in the appropriate section of the eCRF;
- Patient will be discharged and an appointment will be taken for the phone follow-up visit, scheduled after 7 (± 1) days from the procedure.

6.2.2 Phone follow-up - Visit 2 (Day 7 ± 1)

- All concomitant medications being taken by the patient will be checked and, in case of changes from the baseline/treatment visit, will be recorded in the patient's medical records and in the appropriate section of the eCRF;
- The occurrence of general and specific adverse events from the previous visit will be checked and (if any) will be recorded in the patient's medical records and in the appropriate section of the eCRF; Visit 2 (phone follow-up visit) will represent the conclusion of patient's participation in the study.

7. SAFETY

Complete and accurate data on all adverse events (AEs) experienced for the duration of the study reporting period will be reported on an ongoing basis in the AE forms of the eCRF.

It is important that each AE report includes a description of the event, its expectedness, whether it is considered serious, its duration (onset and resolution dates), its intensity, its relationship to the medical device, any other potential causality factors, any action taken and its outcome.

Note: After completion of the investigation, the Sponsor will continue to have an obligation to report serious and treatment-related AEs affecting the investigation subjects.

Refer to Section 7.1.4 for procedures of reporting of serious adverse events (SAEs), devices deficiencies (DD) and medical device incidences.

7.1 Medical Device – Class I

7.1.1 Definition of (Serious) Adverse Events and other safety related events

An Adverse Event (AE) is defined as "any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether related to the investigational medical device".

This definition is restricted to events related to the investigational medical device and includes: events related to the investigational medical device, events related to the study procedures and events related to the device users or to other persons involved.

An **Adverse Device Effect (ADE)** is defined as an AE related to the use of the medical device.

This definition includes any AEs resulting from insufficiencies or inadequacies in the instructions for use, in the deployment, the implantation, the installation, the operation, or any malfunction of the medical device. It also includes any AE resulting from a user error or from the intentional abnormal use (misuse) of the investigational medical device. All ADEs will be classified as Serious/Non-Serious according to the categories of seriousness and as Mild, Moderate or Severe according to the intensity classification. In addition, the investigator will always be asked to express his/her judgment about the causality relationship with the medical device.

Device deficiencies (DDs) are defined as any inadequacy of the medical device with respect to its identity, quality, durability, reliability, safety or performance, including malfunctions, use errors, and inadequate labelling. A malfunction is defined as a failure of the investigational medical device performance compared to its intended purpose, when used in accordance with the instructions for use or protocol. All DDs will be documented during the clinical investigation and reported to the Sponsor on the appropriate form.

A device deficiency not leading to an AE but that could be the cause of a medical occurrence if suitable actions have not been taken, if intervention had not been made, or if circumstances had been less fortunate, must be reported in the same way of an adverse event.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence or effect that:

- Results in death;
- Is life-threatening;

- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important medical event (i.e. important medical reactions that jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition).

The term "life-threatening" in the definition refers to an event in which the subject was at risk of death at the time of the event; on the contrary, it does not refer to an event which hypothetically might have caused death if it was more severe.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but that may jeopardise the patient or may require a medical intervention to prevent one of the other outcomes listed above, should also be considered serious. (ICH E2A).

SAEs should be followed up until resolution or stabilisation. Participants with ongoing SAEs at the moment of their study termination (including safety visit) will be further followed up until recovery or until stabilisation after the study termination.

Any adverse event which does not fall into the above-described categories is to be defined as Non-Serious.

Seriousness must not be confused with the intensity of the event (severity).

Planned hospitalization for a pre-existing condition, or a procedure required by protocol, without serious deterioration in health, is not considered a SAE, but part of the medical history.

Causal Relationship of SAE [MEDDEV 2.7/3 revision 3, May 2015]:

A causal relationship towards the medical device or study procedure should be rated as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Unlikely:** The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

Device deficiencies that might have led to an SAE are always related to the medical device.

Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE. All SADEs will be recorded in this study.

An **Unanticipated Serious Adverse Device Effect (USADE)** is defined as a SADE which by its nature, incidence, severity, or outcome is not identified in the current version of the risk analysis report.

An **Anticipated Serious Adverse Device Effect (ASADE)** is an effect which by its nature,

incidence, severity or outcome has been identified in the current version of the risk analysis report.

A Device Deficiency with SAE potential is a device deficiency that might lead to a serious adverse event if a) suitable actions have not been taken or b) interventions have not been made or c) if circumstances have been less fortunate.

Health hazards that require measures: Findings in the trial that may affect the safety of study participants, and which require preventive or corrective measures intended to protect the health and safety of study participants.

7.2 Method of Recording and Assessing Adverse Events

It is responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questionings (e.g., how have you felt since I saw you last? is there anything new that you wish to discuss?).

All Adverse Events occurring during the clinical investigation (starting from the signature of the informed consent and until the end of the study) must be documented in the patient's medical records and in the Adverse Event forms on the eCRF, irrespectively of their classification; the Adverse Event forms should be completed in English, possibly writing clearly in capital letters. If the eCRF system is not available, the paper SAE reporting form will be filled in (in English language, written in clear capital letters) and reported according to the indications provided in section 7.1.4.

For any adverse event, the following information will be recorded: description of the event, date of onset and date of end, intensity, correlation with investigational product, action taken and outcome.

7.2.1 Intensity of an adverse event

Each Adverse Event will be rated on a 3-points scale of increasing intensity:

- **Mild**: The event causes a minor discomfort, or does not interfere with daily activity of the patient, or does not lead to either modification of investigational product dosage or establishment of a correcting treatment;
- **Moderate**: The event perturbs the usual activity of the patient and is of a sufficient severity to make the subject uncomfortable. Subject is able to continue in study and local or non-invasive treatment for symptoms may be needed;
- **Severe**: The event prevents any usual routine activity of the patient and causes severe discomfort. It may be of such severity to cause the definitive interruption of treatment.

7.2.2 Outcome

Each Adverse Event will be rated by choosing among:

- Recovered/resolved;
- Recovered with sequelae;
- Not recovered;
- Recovering;
- Fatal;
- Unknown.

7.2.3 Medical Device Incidents

According to MEDDEV 2.12-1, Rev. 8, a medical device incident is defined as 'any malfunction or deterioration in the characteristics and/or clinical performance of a device, as well as any inadequacy in the labelling or the instructions for use, which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health'. A medical device incident that would require reporting includes:

a) Serious public health threat: any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action (MEDDEV 2.12-1 rev.8);
b) Death or UNANTICIPATED serious deterioration in state of health of a subject that resulted in:
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;
c) Other events: events that have an established link between the device and the event.

7.2.4 Reporting of (Serious) Adverse Events and other safety related events

All SAEs/SADEs and DDs that could have led to a serious adverse device effect must be reported, whether or not considered causally related to the medical device, or to the study procedure(s). All the above-mentioned events will be recorded in the eCRF no later than 24 hours after acknowledging the occurrence of the event. If the eCRF system is not available, the paper SAE/DD/Device Incidents reporting form will be filled in (in English language, written in clear capital letters) and must be sent via email to the Sponsor at the email address indicated below.

Day 0 is the day the Investigator becomes aware of an event occurred to the subject, and it is used by the Sponsor as reference day for regulatory purposes. Each SAE and SADE must be tracked and assessed by the Sponsor. The Sponsor will report any SAEs/SADEs to the relevant Independent Ethics Committee (IEC) as required by local requirements of the committee and to the Competent Authority. The Sponsor will determine whether a SADE is considered "anticipated" or not. Each DD must be tracked and assessed by the Sponsor. Any DD that might have led to a SAE if suitable action had not been taken or intervention had not been made or if circumstances had been less fortunate will be reported to the Competent Authority.

All SAE/DD/Device Incidents, independently of their causal relationship, must be reported immediately (within 24 hours) in the eCRF SAE form; if the eCRF system is not available, the paper reporting form must be reported immediately (within 24 hours from awareness) via email or Certified Electronic Mail by the Investigator or his delegated to:

Dr. Alessandro Tozzi, Endostart s.r.l., Via delle Regioni 265, 50052 Certaldo (FI), Italy.

Tel: +39 338 7717731

Certified Electronic Mail: euroendoscopy@pec.it

Email: a.tozzi@endostart.com and a.marsano@endostart.com

Initial notification should include:

- Identification of the Principal Investigator: name, address, study center, telephone number;
- Study protocol number;
- Subject's identification (ID number in the study, date of birth, sex, relevant medical history);
- Device name or code, beginning and end of treatment;
- Description of event and its onset;
- Measures undertaken to treat it;
- Opinion of the Investigator about the relation of the event to the tested medical device.

Subjects experiencing SAEs must be monitored until resolution, and acceptable stabilization in the event of chronicity.

In the event of a death, the pathology report will be always requested.

In case of malfunctioning of the medical device, the Investigator will immediately inform the Sponsor by using the same phone and email addresses specified above. The defected medical device will be shipped to the Sponsor, in order to allow all necessary assessments.

In case of malfunctioning of the study medical device, the patient must not be penalized. In order to allow the treatment completion, a set of rescue medical device will be forwarded to each physician.

Once per year for the duration of the research or on request, the Sponsor transmits a safety report with all the available safety information to the Competent Authority (CA) and to the sites involved. This report includes notably the list of all the suspected serious adverse reactions and an analysis of the information regarding the safety of individuals participating in the research.

The Investigator will submit, on request, copies of all reportable SAE reports to the Ethics Committee concerned. Once per year for the duration of the research or on request, the Investigator or its delegated transmits the safety report with all the available safety information to the local Ethic Committee.

7.3 Follow up of (Serious) Adverse Events

Follow-up of SAEs/SADEs/device incidents

- Reporting of SAEs/SADEs/device incidences from the investigational site begins from signing of informed consent and ends at the last study visit/last follow-up contact.
- All new SAEs/SADEs/device incidences occurring beyond this time frame and coming to the attention of the investigator must be recorded only if they are considered (in the opinion of the Investigator) causally-related to the investigational product. Thus, only SAEs/SADEs/device incidences related to the investigational product will be followed after the Visit 2, until resolution, stabilization or patient loss at follow-up.
- Reports of SAEs/SADEs/device incidences occurred during the study or after the site closure should be reported directly from the Investigator to the Sponsor Safety Contact see Section 7.3.4.
- All SAEs/SADEs/device incidences should be followed-up in order to elucidate as completely and practical as possible their nature and/or causality. The follow-up

information should be submitted until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, until progression has been stabilized or until the patient is lost to follow-up. Follow-up may therefore continue after the patient has left the study.

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the Sponsor Safety Contact by email together with the SAE form, retaining a copy on site filing it in the patient folder.
- If an autopsy is performed, copy of the autopsy report should be actively sought by the Investigator and sent to the Sponsor Safety Contact as soon as available, retaining a copy on site and filing it in the patient folder.

8. STATISTICAL METHODS

8.1 Hypothesis

This study is designed to test the null hypothesis that the proportion of 'event' (intended as procedure incomplete or serious adverse event) is equal or greater than 20%. The alternative hypothesis is that the proportion of 'event' is less than 20%. In statistical terms:

$$H0: p \geq 20\%$$
$$H1: p < 20\%$$

Where:

p = true proportion of patients with event

8.2 Determination of Sample Size

Efficacy (first primary objective) will be assessed by measuring the colonoscopy completion rate in long-lasting procedures, which is a measurable parameter of clinical value recognized by international medical societies. Safety (second primary objective) will be assessed by measuring the rare of adverse events. They are classified into: serious gastrointestinal events; myocardial infarction; stroke; pneumonia. Based on the literature [30]; their occurrence rates in screening or surveillance colonoscopy are 47 persons, 4 persons, 7 persons and 10 persons per 100'000, respectively.

These two objectives are merged in one indicator, which is equal to 1 for each subject if the procedure is incomplete or an adverse event occurs, and 0 otherwise.

The non-completion rate of long-lasting colonoscopies conducted with Endorail is expected to be around 10%. This will be compared to the above-mentioned threshold of 20% for incomplete procedures. It should be noted that this threshold is conservative and represents the most critical setting for comparison with respect to the state of the art, as it is derived from the lower bound of the range from the literature.

When including the safety to provide the expected value of the indicator for Endorail and the corresponding threshold, the above values of 10% minimally change, as the adverse event

occurrence rate is 0.068% (given by the sum of the occurrence of the 4 events reported above per 100'000 persons, expressed in percentage).

With a significance level α of 5%, assuming a proportion of outcome of 10.1%, 85 patients allow to test with a power of 80% the H0: $p \geq 20\%$ vs H1: $p < 20\%$, where 20% is the estimated percentage of incomplete procedure from literature.

The chosen number is then increased by the 10% to account for possible drop-out (e.g., cases to be discarded, losses to follow-up, etc.), resulting in 85/0.90 = 95 patients to be actually enrolled.

8.3 Statistical criteria of termination of trial

Interim analyses will be considered, to be able to terminate the study in advance if significance is found. In particular, when 38 patients (40% of the sample size) and 57 patients (60% of the sample size) are reached, the significance will be tested. If significance is found, the trial can be terminated with the patients already collected.

8.4 Planned Analyses

The statistical analysis plan will be finalized before Data Base Lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses.

All data obtained in this study and documented in the eCRFs will be listed and summarized as appropriate:

- for quantitative variables: standard quantitative statistics (N, mean, standard deviation, median, interquartile range, minimum and maximum);
- for qualitative variables: frequency distribution [number of non-missing observations (N) and percentages (%)].

A statistical test will be performed to assess the significant difference of the indicator with respect to the threshold and statistically prove efficacy of Endorail in long-lasting procedures. Due to the type of variable, the exact binomial test will be adopted. Additionally, considering as alternative hypothesis that the rate observed in the analyzed population is less than the respective threshold, the one-tailed test will be adopted.

Medical adverse events and medical device adverse events will be collected during the study.

The number of adverse events (AEs) – related or not to the medical device – and the number and proportion of patients with at least one AE will be presented.

All adverse events will be tabulated by System Organ Class (SOC) and Preferred Term (PT) after medical coding using the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus version 24.1. The primary SOC and the PT will be used for the analysis of the frequency

distribution.

The frequency of occurrence of specific adverse events (gastrointestinal bleedings, intestinal perforation, mucosal petechiae, abdominal pain) will be presented by means of default descriptive statistics.

Statistical analyses will be carried out using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

8.4.1 Datasets to be analysed, analysis populations

- Screening set: will include all patients who have signed the informed consent and have been screened for inclusion in the study;
- Intention-to-treat population (ITT): will include all enrolled patients who have started treatment with Endorail;
- Per-Protocol (PP) population: will include all patients of the ITT who also meet all inclusion/exclusion criteria and who do not have any major protocol deviation, to be defined in a data review meeting (DRM) of the Sponsor, Contract research Organization (CRO) representatives and the biostatistician.

Analysis will be performed on the ITT population and will be repeated in the PP population. The results obtained in the PP population will be seen as confirmative of those observed in the ITT population.

8.4.2 Interim analyses

Two interim analyses will be planned, a first when 40% of the sample size (38 patients) is reached and a second when 60% of the sample size (57 patients) is reached. During these interim analyses the significance will be tested. If significance is found, the trial can be terminated with the patients already collected.

38 patients guarantee a statistical power of 80% if at least 93.9% of these are free of 'event' (intended as procedure incomplete or serious adverse event). 57 patients guarantee a statistical power of 80% if at least 91.8% of these are free of 'event'.

8.5 Handling of missing data and drop-outs

Not applicable. Missing data will not be replaced.

9. QUALITY ASSURANCE AND CONTROL

All participant data relating to the study will be recorded on eCRF. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
The sponsor or its designee is responsible for the data management of this study including quality checking of the data.
The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of participants are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

9.1 Data handling and record keeping / archiving

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

9.1.1 Case Report Forms

The study will be conducted in compliance with the dictates of the Helsinki declaration and in accordance with the rules of good clinical practice (Ministerial Decree of 15/07/1997 and subsequent amendments) as well as with the applicable regulatory provisions.
Each participating center will maintain the medical records and research data of this study in an appropriate manner, in accordance with section 4.9 of the ICH-GCP E6, with the provisions of the regulatory bodies and the institution to which it belongs to ensure the protection of the confidentiality of the patients. As a participant in a clinical study, each center will allow staff authorized by the sponsor and regulatory agencies to review (and when permitted by law, to copy) medical records in order to check the quality of the data, for audits and for evaluations of the study safety and progress.
Source documents are all the information, original records of clinical findings, observations, or other activities of a clinical study necessary for the reconstruction and evaluation of the study itself. Examples of these original documents and records include, but are not limited to, medical records, clinical charts, laboratory notebooks, memos, patient diaries or evaluation lists, data recorded by automated tools, copies or transcripts certified after verification that these are accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, plates obtained with

x-rays, subject cards and records kept in pharmacies, laboratories, and in the technical-medical departments involved in the clinical study.
Data collection is the responsibility of the staff at the center involved in the clinical study under the supervision of the center's Principal Investigator. The electronic data collection form (eCRF) is the main tool for collecting study data. The researcher should ensure the accuracy, completeness, legibility and timeliness of the data reported in the eCRF and in the same way as the other data reported.

The data reported in the eCRF, which derive from source documents, must be identical to the original ones and where this is not the case, the discrepancy must be explained. All data requested by the eCRF must be registered. Any missing data must be explained. Any changes or corrections to a paper CRF (in case the eCRF is not available for any reason) or document must be dated, listed next to the initials of the compiler, explained (if necessary) and must not obscure the original data. The investigator should keep track of the changes and corrections made to the eCRFs.
The institution should maintain the study documents as specified in the essential documents for conducting a clinical study (ICH-GCP E6, section 8) and as required by regulatory bodies and guidelines. The institution should take measures to prevent accidental or premature destruction of the documentation.
Essential documents (written and electronic) should be kept for a period of time not less than twenty-five (25) years from the completion of the study, unless the Promoter provides a written document that allows for the disposal and conservation of data for an additional period of time if permitted by law, regulatory bodies and/or guidelines.
The data will be inserted and managed through the use of the electronic CRF (eCRF) developed through the ICE platform and accessible via a specific URL address that will be provided at the moment of the SIV. To protect security and privacy, only authorized users will be allowed to access the eCRF through the use of individual access credentials (each user will be provided with unique username and password). The login credentials will be generated by the database administrator and communicated to the user via email. The user must change the password at the first access. The password will need to be changed every 3 months.
The data collected will be pseudo anonymized; for each participating subject an alpha numeric code (subject code) will be generated consisting of the center code, a spacer character and the subject number (e.g. CTR 01-01) and the data will be stored electronically. To keep track of the association between the medical record and the subject code, each center will compile a study specific form, as indicated in section 4.4. These forms, if in hardcopy must be kept in a place with limited access and locked, if in electronic form, must be kept in a separate, encrypted (AES-256 encryption) and password protected file; these forms will never be shared with the Promoter, with the database administrator and not even with the study statistician.

9.1.2 Specification of source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, and any discrepancy must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
The source documents for this study will be the patient's paper medical report, where are recorded

all the information needed to complete the eCRF. All the information inserted in the eCRF will be in accordance with the paper medical report. Among the data requested from the eCRF there are demographic data, visit dates, participation in study and Informed Consent Forms, SAEs, AEs, concomitant medication, medical history, and many other results of relevant examinations.

9.1.3 Record keeping / archiving

All study data must be archived for a minimum of 25 years after study termination or premature termination of the clinical trial.
Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period.

9.2 Data management

9.2.1 Data Management System

The CRFs in this trial are implemented electronically using a dedicated EDC system (ICE, Integrated Clinical Trial Environment, Advice Pharma) that fulfils the legal requirements for clinical trials. The EDC system is activated for the user only after successfully passing a formal test procedure. All data entered in the EDC are stored on a Linux server in a dedicated Oracle database.

9.2.2 Data security, access and back-up

The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.
All data entered into the EDC are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date to ensure proper audit-trail. Retrospective alterations of data in the database are recorded by time, table, data field and altered value. A multi-level back-up system is implemented.

9.2.3 Analysis and archiving

At interim and final analyses, data files will be extracted from the database into statistical packages to be analysed. The status of the database at this time is recorded in special archive tables. The study database with all archive tables will be securely stored by Advice Pharma. The sponsor also keeps the Trial Master File and interim and final reports both in electronic and in hard copy for at least 25 years after trial completion. Site will archive the Investigator Site File and Source Data for at least 25 years after trial completion.

9.2.4 Electronic and central data validation

Data is checked by the EDC system for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. In addition, central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data. Data validation process is performed in accordance with the local regulations, with the FDA CFR 21 PART 11, GMP V.4 Annex 11, Data integrity, GAMP5 guideline and Good Practices for Computerized Systems in regulated "GXP" environments. Pharmaceutical Inspection Convention/Pharmaceutical Inspections Co-operation Scheme (PIC/S).

9.3 Monitoring

The study will be monitored on a regular basis by the Sponsor's adequately qualified and trained clinical Monitors throughout the study period to ensure the proper conduct of the clinical Investigation.
The purposes of study monitoring are to verify that the rights and well-being of study subjects are protected, that the reported study data are accurate, complete and verifiable against the source documents, and that the study is conducted in accordance with the current clinical investigation plan, Good Clinical Practice guideline (UNI EN ISO 14155), ICH-GCP E6, 21 CFR 812.28, 21CFR 814, 21 CFR 807, and applicable regulatory requirements.
During the monitoring visits, Monitors will verify the following data, including but not limited to: subject informed consent, subject's eligibility, safety data and reporting, quality of source documents and eCRF data against subject's medical records. If inconsistencies are found, the corresponding corrections to the eCRF data will have to be made by the Investigator or designated person. Monitors will also check subject compliance, delegation of responsibilities within the Investigator's team, relevant communications with family doctors (if any), ancillary equipment and facilities, etc. The Investigator and other site staff involved in the study must allocate enough time to the Monitor at these visits. Additionally, due to the COVID-19 pandemic, site monitoring visits may not be feasible; in that case, a remote monitoring strategy will be implemented.
The Investigator agrees to allow the Sponsor's monitors to have direct access to the study records for review, being understood that they are bound by professional secrecy, and that they will not disclose any personal identity or personal medical information.

9.4 Audits and Inspections

Upon request by the Sponsor, on-site study audits may be conducted in order to ensure the study is in compliance with GCP, applicable regulatory requirements, and the clinical investigation plan. The auditing activities may also be conducted after study completion.
The Investigator agrees to allow the Sponsor/auditors' monitors to have direct access to the study records for review, being understood that they are bound by professional secrecy, and that they will not disclose any personal identity or personal medical information.
Regulatory Authorities may wish to conduct on-site inspections (during the study or after its completion). If a Regulatory Authority notifies the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the Investigator must inform the Sponsor immediately. The Investigator will make every effort to facilitate the conduct of the audits and inspections, giving access to all necessary facilities, data and documents.
Any result or information arising from the inspection will be immediately communicated by the Investigator to the Sponsor. The Investigator will take all appropriate measures required by the Sponsor to implement corrective actions for all problems found during the audits or inspections.

9.5 Ethical considerations

9.5.1 Ethics Committee (EC) and Competent Authority (CA)

Before initiating the trial, the Sponsor should have written favourable opinion from the EC and should have notified the Ministry of Health or the Competent Authority for the trial conduction. All the correspondence with the EC and the Competent Authority should be retained in the Investigator File.

Before implementing any protocol amendment, the EC/Competent Authority written approval must be obtained. The only circumstance in which an amendment may be initiated prior to EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the EC/Competent Authority must be notified in writing as soon as possible.

9.6 Ethical conduct of the trial

9.6.1 Informed Consent

It is the responsibility of the investigator to give each patient (or the patient acceptable representative) full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The patient must be informed about his/her right to withdraw from trial at any time. The patient should have sufficient time and opportunity to enquire about details of the trial and to decide whether or not to participate in the trial.
The patient must be made aware that he/she may refuse to join the study or may withdraw his/her consent at any time without prejudicing further medical care and that he/she is covered by the Sponsor's indemnity insurance in the event of a study related injury.
Written subject Informed Consent Form must be approved by the EC and must be given to each patient before any trial-related procedure is undertaken.
It is responsibility of the investigator to obtain the Informed Consent Form signed and dated by the patient and by the medical person conducting the Informed Consent discussion, prior to undertake any trial-related procedure, in accordance with the UNI EN ISO 14155 and the current version of the Declaration of Helsinki. One copy of the signed and dated Informed Consent Form should be given to the patient. The originally signed document should be archived in the appropriate section of the Investigator Site File.
The approved patient Informed Consent Form must not be changed without prior approval by the Sponsor and by the EC.
When new study information arises during the study, the patients still participating must be informed and a new Informed Consent Form or an addendum to the already signed Informed Consent Form must be signed and dated by the patients, after the approval by the EC.
The patients must also know that their personal medical records may be reviewed in confidence by the Sponsor's staff or representatives and by the Ministry of Health and the EC and that every personal information will be collected and retained in a confidential database.
If a patient becomes incompetent during the course of the trial, where it was not anticipated, legally acceptable representative authorization should be obtained for a subject's participation continuation.

9.7 Confidentiality, Data Protection

Apart from site staff, also Sponsor/Regulatory Agency monitors, auditors or inspectors will have direct access to medical records and source documents for review during and after the study, being understood that they are bound by professional secrecy, and that they will not disclose any personal identity or personal medical information.

10. INSURANCE

Insurance will be provided by the Sponsor. A copy of the certificate is filed in each investigator site file and the trial master file.

11. PUBLICATION AND DISSEMINATION POLICY

All information obtained as a result of the study will be regarded as confidential. The results of the clinical study will be documented in an integrated clinical study report according to UNI EN ISO 14155 and to the ICH-GCP E6.
The Sponsor and the Investigator(s) agree that no publications presenting or discussing data and/or results from this clinical study sponsored by Endostart srl. will take place until the the data have been interpreted, and the interim or final report has been issued.
As a rule, the Sponsor is free to use the data collected in the sponsored study for world-wide scientific product documentation, and for publication.
In general, the Sponsor has no objections if the Investigator publishes the results of the study. However, the Investigator is requested to provide the Sponsor with a copy of the manuscript for review before submitting it to the publisher with a cover letter informing the Sponsor about the intention to publish the study results. When permission for presentation or for publication is granted, Investigators, prior to submission of a manuscript or abstract to the publisher, shall forward a copy of said manuscript or abstract to the Sponsor who shall have 45 days to request any reasonable amendment thereto, which shall be taken into due account and consideration by the Investigator.
The Sponsor is entitled to include, as authors of the publication, all Sponsor's personnel who contributed substantially to the theoretical or experimental work and also to take part in the decision that establishes the order in which the authors' names will be given. Costs for publication must be regulated by written agreement between the parties.
If publication of the results of the study, either in part or in full, is prepared by the Sponsor, the Investigator(s) will be provided with a copy of the manuscript before the submission to the publisher and asked to give approval of the document. The Investigator will be asked in writing if he/she accepts to be included as author of the publication. Answers should be sent in writing to the Sponsor within a reasonable time limit (30 days). If no answer is received, it is assumed that the Investigator agrees to the Sponsor's proposal.

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