ISOCLINICAL INVESTIGATION PLAN

Introduction of EndoSign ® in management of Barrett's oesophagus - a Swedish feasibility study

Version number:	1.1
Date:	2023-11-29
Sponsor:	Västra Götalandsregionen (VGR)
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Revision history

Document version	Date of Issue	Summary of Change
1.0	2023-07-01	
1.1	2023-11-29	Minor changes inclusion and exclusion criteria More details about endoscopy procedure

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Signatures

Sponsor
I am responsible for ensuring that this CIP includes all essential information to be able to conduct this clinical investigation. I will submit the CIP and all other important clinical investigation-related information to the responsible investigator(s) so that they can conduct the clinical investigation correctly. I am aware that it is my responsibility to hold the staff members who work with this clinical investigation informed and trained.

Sponsor's signature Date

Printed name

Coordinating Investigator

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical investigation. By signing my name below, I agree to conduct the clinical investigation in compliance with this Clinical investigation plan, the Declaration of Helsinki, SS-EN ISO14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical investigation.

I will submit this CIP and all other important clinical investigation-related information to the staff members and investigators who participate in this clinical investigation, so that they can conduct the clinical investigation correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this clinical investigation informed and trained.

I am aware that quality control of this clinical investigation will be performed in the form of monitoring, audit, and possibly inspection.

Coordinating Investigator's signature Date

Printed name

Principal Investigator

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical investigation. By signing my name below, I agree to conduct the clinical investigation in compliance with this Clinical investigation plan, the Declaration of Helsinki, SS-EN ISO14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical investigation.

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I am aware that quality control of this clinical investigation will be performed in the form of monitoring, audit, and possibly inspection.

Site

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Funding and research agreement

This clinical investigation is initiated by academic researchers. The sponsor pays for overall costs of the study, e.g. application costs, costs for data management and some material costs. Each site pays for its material, laboratory analysis, premises and personnel costs. Some material and laboratory costs are funded by Cyted Laboratorium.

List of used acronyms and abbreviations

Abbreviation	**Term/Explanation**
ADE	Adverse Device Effect
AE	Adverse Event
BE	Barrett's oesophagus
CIP	Clinical Investigation Plan
CRF	Case Report Form
DD	Device Deficiency
DMC	Data Monitoring Committee
EMR	Endoscopic Mucosal Resection
ESCC	Esophageal squamous cell carcinoma
ESD	Endoscopic Submucosal Dissection

GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
IB	Investigator's Brochure
IFU	Instructions for Use
IM	Intestinal metaplasia
SS-EN ISO	Swedish Standard - European standard International Organization for Standardization
ITT	Intention-to-treat = including all data from all subjects who have participated in the clinical investigation
MDCG	Medical Device Coordination Group
PMCF	Post-Market Clinical Follow Up
PP	Per Protocol analysis = including only data from subjects who have completed the clinical investigation completely in accordance with the CIP, with no deviations from the CIP
RFA	Radiofrequency ablation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual analog scale

1. Synopsis

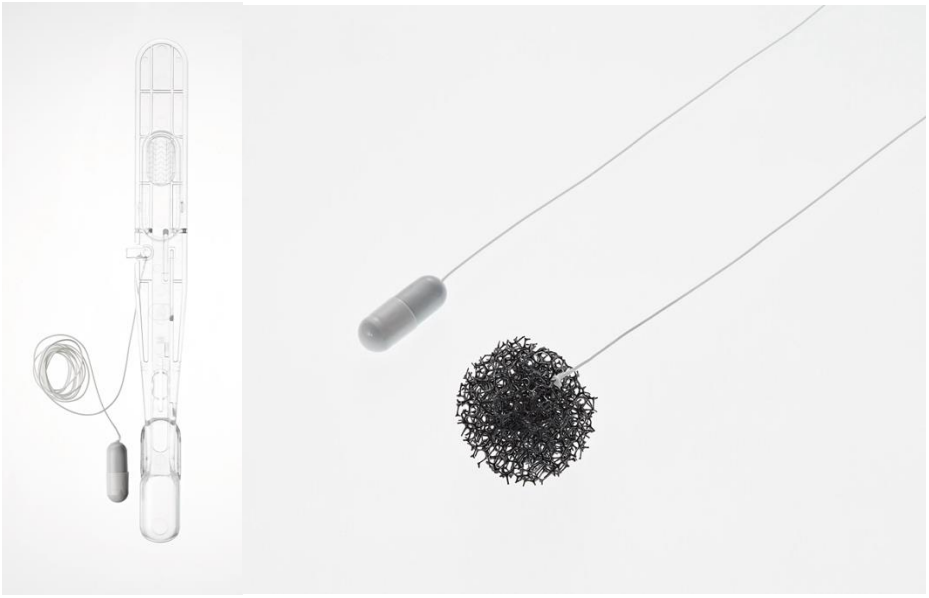
Background and rationale:	
Investigational device:	EndoSign® Cell collection device
Number of subjects:	75 (15 per site)
Inclusion criteria:	● Patients with histopathologically confirmed diagnosis (intestinal metaplasia) of Barrett's oesophagus (BE) and at least C0M1 ● Active monitoring with planned surveillance endoscopy within 3 to 12 months ● Age: 18 – 84 years
Exclusion criteria:	● Scheduled for other endoscopic treatment (e.g. ablation) at the next surveillance endoscopy ● Alarm symptoms ○ Dysphagia and/or food sticking ○ Dyspepsia and weight loss ○ Dyspepsia and anaemia ● Patient with a diagnosis of an oropharyngeal, oesophageal or gastro-oesophageal tumour ● Patient who has had treatment to the oesophagus e.g. endoscopic mucosal resection, endoscopic submucosal dissection, radio frequency ablation, surgery within the previous two months ● Patient known to have gastric or oesophageal varices or cirrhosis of the liver ● Patient with a known anomaly of the oesophagus e.g. webbing, pouch, stricture etc ● Patients unable to give consent ● Patients who have had a stroke or any other neurological disorder where their swallowing has been affected ● Patients who have had a myocardial infarction in the last 3 months ● Patients who have had fundoplication or other surgery to oesophagus and proximal stomach ● Patients using anti-trombotic drugs which cannot be temporarily discontinued

Study objectives:	• To determine whether it is feasible to use EndoSign ® Cell collection device in patients with Barrett's oesophagus under surveillance • Acquire data and experience to assess whether it is possible to perform a full scale study in the future and identify what design modifications are needed • Determine steps necessary for implementation in secondary care.
Study endpoints:	• Acceptability • Safety • Assess the feasibility of recruitment • Implementation in secondary care • Data collection method and outcome measures • Preliminary evaluation of histopathological results
Planned duration of the clinical investigation:	*Q4 2023 – Q3 2024*

2. Identification and description of the investigational device

2.1. Description of the investigational device

EndoSign® Cell collection device is a CE-marked non-endoscopic cell collection device used to detect Barrett's oesophagus, early cancer and other oesophageal conditions. It consists of a tethered sponge in a gelatine capsule attached to a string that is swallowed and when removed from the stomach, it collects cells along its way. The sample is then put into a preservative which is stable at room temperature. It is processed in a central laboratory and can be assessed for Barrett's biomarker Trefoil Factor 3 (TFF3), atypia and will be stained for p53 as an indicator for dysplasia or cancer.



2.2. Intended purpose

The EndoSign® cell collection device is to be used for the collection of cells from the surface of the oesophagus for molecular, cytological, and histological analyses.

The investigational device is CE marked and will be used according to its intended purpose in this clinical investigation.

2.3. Manufacturer of the investigational device

Name: Cyted Ltd
Address: 22 Station Road, Cambridge, CB1 2JD United Kingdom
Contact: +1 508-261-8000

2.4. Model/type

Generic denomination: Cell Collection Device
Device name: EndoSign® Cell collection device
Device trade name: ES-CYT-102
Model: Not applicable
Medical device classification: Class I
European Medical Device nomenclature: A99 (Devices for administration, withdrawal and collection- other)

2.5. Target population

Target Population: Patient’s aged 18 and over

Intended User Group: The EndoSign® Cell collection device is to be administered by trained healthcare professionals such as medical doctors, registered nurses, and other qualified health professionals trained in use of the device

2.6. Detailed description of the investigational device and materials coming into contact with the human body

See Appendix A – EndoSign® Cell collection device instruction manual

2.7. Medical or surgical procedures

See Appendix A – EndoSign® Cell collection device instruction manual

2.8. Summary of required training/experience needed

Any personnel administering the EndoSign® will undergo a training webinar and in person training until they are signed off as competent (usually 8-10 procedures).

2.9. Background

The incidence of esophageal adenocarcinoma has increased dramatically in the Western world in recent decades [1]. Barrett's oesophagus is a premalignant condition with an approximately 0.3% annual risk of developing into adenocarcinoma[2]. Globally, Esophageal squamous cell carcinoma (ESCC) still accounts for 90% of new cases of esophageal cancer[3], but in Sweden, adenocarcinoma is more common.
Symptomatic oesophageal cancer has a poor prognosis as the disease is often detected in late stages. However, the prognosis for early/superficial cancer is very good.
According to epidemiological studies the prevalence of Barrett's oesophagus is between 0,5 - 2%. [4] Less than 10% of patients resected for adenocarcinoma have previously been diagnosed with Barrett's oesophagus[5] and therefore in most cases of esophageal adenocarcinoma there has been no way to prevent progress.
There are now good endoscopic treatments for dysplasia and early cancer, such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and radiofrequency ablation (RFA).

Patients diagnosed with Barrett's oesophagus are usually included in a surveillance program according to European guidelines [6]. Surveillance intervals are stratified according to BE lengths. Studies have shown that surveillance leads to earlier detection of cancer and improved survival[7, 8]. Endoscopic surveillance is an invasive method with high costs. Some patients have difficulty tolerating upper GI endoscopy, which can therefore lead to discomfort, stress and anxiety.[9]. There is a reason to believe that the number of surveillance endoscopies in patients at low-risk of developing cancer can be reduced. On the other hand, high-risk patients should undergo intensified follow-up and treatment in tertiary referral centers.

There is currently no evidence that general screening for BE lowers mortality in EAC and endoscopic screening for Barrett's oesophagus is only considered in high risk groups. [6, 10]

The EndoSign® is a CE-marked non-endoscopic cell collection primarily used for the detection of Barrett's oesophagus, early cancer, and other oesophageal conditions such as eosinophilic esophagitis. The device is composed of a tethered sponge housed within a HPMC capsule, which is connected to a string for easy retrieval.

When swallowed and subsequently pulled out of the stomach, it gathers cell samples along its path. These samples are then preserved in a room temperature stable medium. They are subsequently sent to a central laboratory for processing and can be analysed for Barrett's biomarker Trefoil Factor 3 (TFF3), atypia, and stained for p53, which serves as an indicator for dysplasia or cancer.

The EndoSign®'s cell collection, sample processing, and analysis capabilities parallel those of the previously used Cytosponge. Cytosponge-TFF3 test has been shown to detect Barrett's oesophagus effectively. A review of 5 studies underscored the safety and high patient acceptability of this procedure [11]. Remarkably, over 90% of patients succeed in swallowing the Cytosponge on the first try with no serious adverse events reported to date. The risk of detachment is minimal, being less than 1:5,000, and the most common side effect is a sore throat

Iqbal et al showed in a systematic review that Cytosponge-TFF3 detects Barrett's oesophagus with a sensitivity and specificity of 81% and 91%, respectively. [12]

EndoSign® is a new cell collection device was recently introduced and is currently being evaluated in the Cytoprime 2 project. Based on the equivalency claims to the Cytosponge™ (see Appendix B), the device has been adopted for routine use by National Health Services, England. The EndoSign capsule sponge is:

- Simple for practitioners to use, streamlining training and clinic delivery
- Quick to administer, reducing the time taken for the procedure
- Designed to be easy to swallow, improving patient experience
- Affordable with a cost reduction per unit compared to Cytosponge™
- Safe during withdrawal due to tvalidated and improved mechanical properties of the thread attachment.

2.10. Rationale of study

When it comes to surveillance of Barrett's oesophagus, there is a need to enhance the clinical pathway and streamline the use of resources. There is also a reason to evaluate and introduce alternative surveillance methods that are better tolerated by patients. Cell collection device with sponge can be one such method, EndoSign® has not yet been used in Swedish healthcare and the method therefore needs to be evaluated in our setting. The similar cell collection device Cytosponge have been used as a triage tool, patients under surveillance could be divided into various risk groups. This might direct medical interventions toward people who are most at risk of developing cancer. In the future, Cell

collection device with sponge might be used to screen patients with gastroesophageal reflux disease (GERD) for Barrett's oesophagus.

In order to be able to conduct high-quality research on Barrett's oesophagus, a sufficiently large patient base is needed. Both regional and county hospitals conduct surveillance, so it would be advantageous if they all collaborated in future research on Barrett's oesophagus in Sweden.

With this feasibility study, it is possible to introduce and assess EndoSign® within the Swedish Barrett network at a number of hospitals in a controlled manner, which can serve as a crucial foundation for carrying out larger multi-center studies in the future.

3. Risks and clinical benefits of the investigational device and clinical investigation

3.1. Expected clinical benefits

Early detection of oesophageal cancer is the single most important factor in improving the outcome of treatment. This is made possible by identifying patients at risk of developing oesophageal cancer and following these in a surveillance protocol.

Today, no screening is being conducted for Barrett's oesophagus but this is debated. ESGE guidelines recommend screening of high-risk patients. Cell collection device on a sponge, such as Cytosponge-TFF3, has shown promising results in targeted screening of Barrett's oesophagus in patients with GERD.

Surveillance of Barrett's is conducted with repeated endoscopies where the quality depends on the experience and skill of the endoscopist. There are studies that have shown that endoscopists to varying extent fail to adhere to recommended guidelines regarding e.g. how biopsies should be taken.

The availability of endoscopy differs between hospitals and has been generally limited during the COVID-19 pandemic. Surveillance is costly and with the implementation of cell collection device with sponge it could be possible to re-design clinical pathways and reduce the number of endoscopies needed, which would also increase availability. Most patients will not develop cancer and it would be desirable to prioritize endoscopy resources to the patients who benefit the most.

Cytosponge-TFF3 has been used as a triage to prioritize patients to endoscopy.[13] There is a need to study and validate whether the use of sponge devices coupled with TFF3-analysis in surveillance can improve surveillance, reduce resource utilization and improve outcomes in patients. This feasibility study is an important first step in order to be able to conduct larger studies in the future.

TFF3- analyses of the cell materials from the sponge is performed by Cyted laboratory in the UK and there is reason to evaluate how the logistics of this work.

3.2. Anticipated adverse device effects

Potential complications include: Mucosal laceration or perforation requiring secondary intervention, Bleeding, Aspiration, Intestinal obstruction, Tissue damage, Dysphagia, Pain, Sore throat., Dyspepsia indigestion reflux, Oesophageal or gastric pain, Nausea or vomiting, Voice disturbance, Diarrhoea or an upset stomach, Chest pain or discomfort, Vasovagal attack. Headache, Hernia, Detachment of the sponge.

3.3. Risks associated with participation in the clinical investigation

Participation in the clinical investigations means that the subject will undergo at least one EndoSign® test and a gastroscopy, which entails (albeit a small) risk of complications.

3.4. Steps to be taken to control or mitigate risks

The clinical investigation is conducted in hospitals, which are well-equipped to handle any complications or unexpected results. Healthcare professionals leading the study sessions are knowledgeable about the research project and the treatments being used.

3.5. Rationale for benefit-risk ratio

The advantages for the individual subject are an in-depth investigation (in addition to surveillance) of Barrett's esophagus where the EndoSign® coupled with TFF3-analysis can detect atypia, dysplasia and early cancer.

In the long term, this and future studies can potentially improve the quality of surveillance and treatment of Barrett's esophagus.

4. Objectives and hypotheses of the clinical investigation

4.1. The purpose of the clinical investigation

- To determine whether it is feasible to use EndoSign® with TFF3 analysis coupled with p53 and atypia in patients with Barrett's oesophagus under surveillance
- Acquire data and experience to assess whether it is possible to perform a full scale study in the future and identify what design modifications are needed
- Determine steps necessary for implementation in secondary care.

4.2. Objectives and endpoints

Objective	Endpoint	
To assess patient acceptability for EndoSign®	i. EndoSign® test experience compared to upper GI endoscopy ii. EndoSign® swallowing failures iii. Willingness to undergo EndoSign® again	i. Adapted ENDOPREM and a visual analog scale to rate experience ii. Number of patients that are unable to swallow and attempts made iii. Questionnaire
To assess safety of EndoSign® in secondary care	i. Rates of adverse events up to 7 days after EndoSign® test	i. All adverse events reported during procedure, ER-visits and 7-day follow up.
To assess the feasibility of recruitment	i. Proportion of eligible patients who participate ii. Quantify the number of patients that potentially can be recruited	i. Patients accepting invite and consent divided by total of patients invited ii. Number of patients in surveillance per site
To assess the implementation of EndoSign®	i. Costs and resources required to introduce EndoSign® in secondary care ii. Determine technology and equipment needs and training iii. Clinical staff experience and acceptability of EndoSign® in regards of training, skills, reliability, side effects and user information	i. Interviews with staff and healthcare professionals ii. Equipment needed per session iii. Number of sessions needed until fully trained. iii. Interview with clinical staff iv. Number of days from samples are sent to laboratory in UK until test results arrive

	iv. Logistics of TFF3-analysis of EndoSign® and response times	
To evaluate data collection method and outcome measures	i. Feasibility of questionnaires ii. Response rate for questionnaires iii. Withdrawal and drop-out rates iv. Follow-up rates	i. Validate adapted ENDOPREM ii. The proportion of patients who completes each questionnaire iii. The proportion of patients who, for various reasons, do not complete the study iv. The proportion of patients who complete the follow-up
Preliminary evaluation of results and patient outcomes	i. Demographics of the patient group ii. Patient reported outcome, questionnaire iii. EndoSign® -TFF3 test results (atypia, p53 status, TFF3 status) iv. Number of inadequate samples v. Classification of patients into different risk groups and show preliminary results when used as triage method vi. Results from endoscopy and biopsies and compare to EndoSign® test results	i. Data collected and reported in the CRF collected at first visit ii. VAS, adapted ENDOPREM, EQ-5D iii. Proportion of patients with adequate sampling with positive test iv. Reason for not generating result v. Number of patients categorizes into low, moderate and high risk according to p53 and atypia, combined with clinical factors age, sex, length of segment. vi. Length of BE-segment, visible lesion, intestinal metaplasia, low-grade dysplasia, high grade dysplasia

5. Design of the clinical investigation

5.1. General information

This clinical investigation is designed as a single-armed multi-center feasibility study and is expected to be conducted 2023/2024. The aim is to include 15 consecutive patients per site (75 patients in total) attending routine endoscopy in Barrett's esophagus surveillance.

5.2. Settings and locations

The study will be conducted at the following hospitals:

- Sahlgrenska University Hospital, Gothenburg
- Karolinska University Hospital, Stockholm
- Skåne University Hospital, Lund
- Ersta Hospital, Stockholm
- Vrinnevi Hospital, Norrköping

5.3. Study timetable

Estimated subject enrollment start Dec 1st 2023
Estimated last enrollment: April 1st 2024
Last follow up: Oct 31st 2024

5.4. Subjects

5.4.1.

Inclusion criteria

- Patients with histopathologically confirmed diagnosis (intestinal metaplasia) of Barrett's oesophagus (BE) and at least C0M1

5.4.2.

- Active monitoring with planned surveillance endoscopy within 3 to 12 months
- Age 18 – 84 years

Exclusion criteria (any of the following)

- Scheduled for other endoscopic treatment (e.g. ablation) at the next surveillance endoscopy
- Alarm symptoms
  - Dysphagia and/or food sticking
  - Dyspepsia and weight loss
  - Dyspepsia and anaemia
- Patient with a diagnosis of an oropharyngeal, oesophageal, or gastro-oesophageal tumour

- Patient who has had treatment to the oesophagus e.g. endoscopic mucosal resection, endoscopic submucosal dissection, radio frequency ablation, surgery within the previous two months
- Patient known to have oesophageal varices or cirrhosis of the liver
- Patient with a known anomaly of the oesophagus e.g. webbing, pouch, stricture etc.
- Patients unable to give consent
- Patients who have had a stroke or any other neurological disorder where their swallowing has been affected
- Patients who have had a myocardial infarction in the last 3 months
- Patients who have had fundoplication or other surgery to oesophagus and proximal stomach
- Patients using anti-trombotic drugs which cannot be temporarily discontinued

5.4.3. Investigation population

75 (15 patients per site)

5.4.4. Criteria and procedures for subject withdrawal or discontinuation.

All study participants may discontinue their participation in the study at any time without this affecting their continued surveillance and future treatments. Collected data for the patient will be retained or destroyed depending on the patient's desire

5.4.5. Subject enrolment

A nurse or physician identifies eligible patients to undergo a gastroscopy as part of Barrett's oesophagus surveillance. These patients are asked for participation in the study via an invitation letter or telephone call. Interested patients will be provided with written information about the study and EndoSign® information leaflet. If the patient chooses to participate, written informed consent will be obtained and stored locally. Each secondary care clinic will maintain an anonymized screening log that lists all screened patients. Recruitment continues until 75 patients are included.

5.5. Description of the clinical procedures and diagnostic methods relating to the clinical investigation

5.5.1. EndoSign® test procedure

Study patients are referred to a separate visit to undergo the EndoSign® test. They will be required to refrain from food and liquids for 3–4 hours before the visit and they will respond to a socio-demographic- and clinical form and assessment of symptoms and EQ-5D.

The EndoSign® is administered by a nurse or healthcare professional that has undergone adequate procedure training. The procedure time is 7 minutes with an overall clinic session taking about 20- 30minutes in total.

The patient is asked to swallow the EndoSign® capsule together with some water. The end of the suture is attached to an applicator which the nurse hands to the patient to hold. The capsule will be in the patient's stomach for around 7minutes until it dissolves completely, allowing the sponge to expand to its full size. The sponge is withdrawn by the nurse using the suture. The patient can choose to get local anaesthetic spray into their throat before the sponge is removed. The sponge is then placed in a sample collection kit provided by Cyted and secured with a patient number identification label.

The patient will be instructed to try again if they are unable to swallow the capsule the first time. Before being labelled as "EndoSign® swallowing failure," patients will have a maximum of two failed attempts.

After 30 minutes, patients are asked to answer forms about anxiety level and procedure-specific questions to evaluate acceptability. The visual analog scale (VAS) and a quick questionnaire using the adapted ENDOPREM measure will be used.

5.5.2. Endoscopy

The subject is called to a surveillance endoscopy according to previous planning and undergo a standard upper GI endoscopy in accordance with ESGE guidelines. It can be performed with or without sedation.

Diagnostic endoscopic landmarks for BE will be recorded written and with photo documentation.

Biopsies will be taken according to a strict protocol including biopsies from the cardia. Mapping biopsies will be taken every 2 cm for all endoscopies where BE is discovered (in all 4 quadrants) according to the Seattle surveillance protocol. In addition, endoscopically-suspicious areas will be targeted for biopsies.

After 30 minutes, patients are asked to answer forms about anxiety level and procedure-specific questions to evaluate acceptability. The visual analog scale (VAS) and a quick questionnaire using the adapted ENDOPREM measure will be used.

The pathologist will process and examine each biopsy sample in accordance with standard clinical practice. Cases with dysplasia will be reviewed and discussed with an additional pathologist. When reviewing the biopsy data, the pathologists will be blinded to the result of the EndoSign® test.

Participants will receive a letter from the endoscopist informing them of the endoscopy results in the usual manner.

Follow-up

At follow-up, 7 and 90 days after both EndoSign® test and endoscopy, questionnaires and forms (adapted ENDOPREM, VAS, EQ-5D) will be sent to the patient either by mail or as a survey via REDCap.

5.5.3. When the EndoSign® -TFF3 results arrive, these are filled into the database and a standardized feedback letter is sent to the patient with the test result. Patients will be given the option to phone the nurse administering the test for more information. If the cytology test result indicates atypia or dysplasia (p53 positive), the patient is called for a gastroscopy within 2 weeks and otherwise the patient will continue to be followed according to the previous surveillance regimen.

Adverse events

5.5.4. The research nurse will notify the endoscopist immediately if there is a EndoSign® detachment or other adverse event. A qualified healthcare expert would immediately remove the EndoSign® in the never-reported but theoretically possible case of inhalation.

Subjects receive emergency contact information to be able to quickly make contact in the case of adverse events.

5.5.5. Flow chart

Table 1

Procedure	Visit 1 - EndoSign®	Follow-up, 7 day and 90 days	Visit 2 – Gastroscopy	Follow-up, 7 and 90 days
Incl/exclusion criteria	√			
Informed consent	√			
Medical history/ concomitant medications	√			
Patient reported outcome (VAS, ENDOPREM)	√	√	√	√
Questionnaire, EQ-5D	√	√	√	√
Adverse Events	√	√	√	√
Clinical investigation end				√

6.9 End of the clinical investigation

The clinical investigation ends when the last subject has completed the last follow-up. The sponsor will notify the Swedish Medical Products Agency within 15 days after the end of the clinical investigation and send the clinical investigation report within 1 year after the end of the clinical investigation including an easily understandable summary.

6.10 Biological sampling procedure

6.10.1 Handling, storage, and destruction of biological samples

The TFF3-samples are handled and analysed in accordance with a specified SOP and transported directly from the hospital to the central laboratory (Cyted) in the UK. The samples will be pseudonymized according to the specific clinical performance study identification number. Each sample will be processed using H&E (hematoxylin and eosin) and TFF3 immunohistochemistry. In all cases where atypia is detected, a p53 staining will be performed as an indicator of significant pathology. All samples will be analysed within six months and destroyed immediately after the analysis.

A special material transfer agreement will be drawn up for each hospital so that the samples can be sent and analysed in the UK (outside the EU). This information will also appear in the consent documents.

6.10.2 Biobank

This study is covered by the exception rule in the Biobank Act, which means that the Biobank Act does not apply to samples intended for research and which are analyzed within six months of the time of sampling and destroyed immediately after the analysis. Therefore, no biobank agreement will be signed, and no samples will be registered and/or stored.

6.11 Monitoring plan

The clinical investigation will be monitored by an independent monitor before the clinical investigation begins, during the clinical investigation conduct, and after the clinical investigation has been completed, so as to ensure that the clinical investigation is carried out according to the CIP and that data is collected, documented, and reported according to SS-EN ISO 14155:2020 and applicable ethical and regulatory requirements. Monitoring is performed as per the investigation’s monitoring plan and is intended to ensure that the subject’s rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.

7 Statistical considerations

7.1 Sample size justification

The sample size needs to be in the upper range of what is typical in feasibility studies because the studies are conducted at multiple hospitals. 75 patients in total, or 15 patients per hospital, are considered to be enough to determine the feasibility of EndoSign®.
A formal power calculation or sample size calculation is not necessary for this study because accuracy and effectiveness of the technology will not be evaluated.

8 Data management and protection

Data for all subjects who participate in the clinical investigation are coded with a specific clinical investigation identification number. All subjects are registered in a subject identification list (subject enrolment and identification list) that connects the subject's name and personal number with a clinical investigation identification number.
All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification.

8.1 Case Report Form

All data will be anonymized and stored in an electronic study database (e-CRF) using REDCap. The following data will be collected and reported directly in the CRF:

- Sex, age, BMI
- Smoking / Alcohol consumption
- Use of PPI or other acid suppressants
- Year of diagnosis
- Prague classification according to previous endoscopy
- Previous dysplasia
- Previous endoscopic treatments
- Patient-reported experience measurement data (ENDOPREM, VAS)
- Questionnaire results (including EQ-5D)
- EndoSign® -TFF3 test results
- Gastroscopy results (including biopsy results)
- Adverse events

Both written and electronic changes or corrections on CRF will be dated, initialed and explained (if necessary)

8.2 Archiving

The PI and sponsor will maintain the essential clinical investigation documents in the investigation site files archive and sponsor files archive, respectively. The sponsor shall keep all documentation and data for at least years after the clinical investigation has ended. The PI will archive all local investigation documentation for at least 10 years in accordance with Swedish law (Chapter 10, LVFS 2011:19). All documentation and data

will be stored at the Department of Surgery at Sahlgrenska University hospital, Gothenburg.

8.3 Data protection

If any part of the data is handled by any other organization, inside or outside the European Union, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (EU ordinance 2016/679, GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form shall comply with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their clinical investigation data will take place. The subject information and the informed consent form will explain how clinical investigation data are stored to maintain confidentiality in accordance with national data legislation. All information processed by the sponsor will be pseudonymized and identified with Study-ID.

The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the clinical investigation, including the subject's medical history.

9 Amendments to the CIP

Amendments to the CIP will be agreed upon between the coordinating investigator and the sponsor. Substantial modifications must be approved by the Swedish Ethical Review Authority and/or the Swedish Medical Products Agency (as applicable) before implementation.

10 Deviations from the CIP

Investigator(s) are not allowed to deviate from the CIP except if it is for the protection of the subject´s rights, safety, or well-being under emergency circumstances. All such deviations shall be documented and reported to the sponsor, the Swedish Medical Products Agency and/or the Swedish Ethical Review Authority (as applicable) as soon as possible.
All deviations shall be documented with an explanation and reported to the sponsor. Deviations will be reviewed by the sponsor and reported to the appropriate regulatory bodies as required.

11 Device traceability and accountability

The investigational device(s) will only be used in the clinical investigation and according to the clinical investigation plan. The sponsor provides the site with written instructions and technical support.
The investigator will keep records to document the physical location of all investigational devices from shipment to return/disposal. This record should include: name(s) of clinical investigation personnel who received, used, returned, or disposed the device, the date of receipt, identification and quantity of each investigational device (batch number/serial number or unique code), the expiry date, the date or dates of use, subject study-ID, date on which the investigational device was returned, the date of return of unused, expired or malfunctioning investigational devices, and the date and documentation of disposal of the investigational devices as per instructions of the sponsor.

12 Statements of compliance

12.1 Compliance to the investigational plan, good clinical practice, and regulations

The clinical investigation will be conducted in accordance with GCP, the clinical investigation plan, the ethical principles of the Declaration of Helsinki, the principles of SS-EN ISO 14155:2020 and current national and international regulations governing this clinical investigation. This is to ensure the safety and integrity of the subjects as well as the quality of the data collected.

12.2 Ethical review of the clinical investigation

The clinical investigation will commence when written approval/favorable opinion from the Swedish Ethical Review Authority has been received and at least 30 days has passed since the notification was confirmed by the Swedish Medical Products Agency.
The final version of the informed consent form and other information provided to subjects, must be approved or given a written positive opinion by the Swedish Ethical Review Authority and/or the Swedish Medical Products Agency. The Swedish Ethical Review Authority and the Swedish Medical Products Agency must be informed of any changes in the CIP in accordance with the current requirements.

12.3 Insurance

According to the Patient Injury Act, voluntary subjects are equated with patients. The Swedish healthcare regions have signed a patient insurance with Landstingens Ömsesidiga Försäkringsbolag, LÖF

13 Informed consent process

13.1 General process for informed consent

The principal investigator shall ensure that the subject is given full and adequate oral and written information about the clinical investigation, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the clinical investigation at any time without having to provide a reason. Subjects shall be given the opportunity to ask questions and be allowed time to consider the provided information and participation in the clinical investigation. If the person chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as a copy of the informed consent form shall be provided to the subject. The subject's signed and dated informed consent must be obtained before performing any activity specific to the clinical investigation. The process shall be documented in the subject's source documents and the signed informed consents shall be maintained with the essential documents. If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form. If new information is added to the clinical investigation, the subject has the right to reconsider whether he/she will continue their participation.

14 Adverse events, adverse device effects and device deficiencies

14.1 Definitions

14.1.1 Adverse Event

An Adverse Event (AE) is untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.
This definition includes events that are anticipated as well as unanticipated events
This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

14.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is any AE related to the use of an investigational medical device.
This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
This includes 'comparator' if the comparator is a medical device.

14.1.3 Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:

i. life-threatening illness or injury,
ii. permanent impairment of a body structure or a body function,
iii. hospitalization or prolongation of patient hospitalization,
iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
v. chronic disease,

c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect

14.1.4 Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.
SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device shall not be considered Serious Adverse Device Effects.

14.1.5 Unanticipated Serious Adverse Device Effect

An Unanticipated SADE is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device shall be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device shall not be considered Serious Adverse Device Effects.
For the anticipated adverse device effects, se section 4.2 above.

14.1.6 Device Deficiency

A Device Deficiency (DD) is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

14.2 Recording and Reporting

14.2.1 Recording

The principal investigator or an authorized designee will record:

- all AEs
- all SAEs;
- all DDs;
- any new finding in relation to any of the above-mentioned events.

14.2.2 Reporting

The investigators will report all SAEs and DDs to the sponsor, immediately but not later than 3 calendar days after investigation site study personnel's awareness of the event.
The sponsor will report to the Swedish Medical Products Agency all of the following reportable events:

- any SAE that has a causal relationship with the investigational device or the investigation procedure, or where such causal relationship is reasonably possible;
- any DD that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; and
- any new findings in relation to any event referred to above.

Reporting by the sponsor will be done by filling out the "Summary Reporting Form" (MDCG 2020-10/2). The form will be filled in/updated for each reportable event or for new findings/updates to already reported events. The form will be transmitted to the Swedish Medical Products Agency. For events that indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it will be reported immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. Any other reportable events or a new finding/update to it will be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

14.2.3 Assessment of Causality

The relationship between each adverse event and the investigational device, the comparator and the investigation procedure will be assessed and recorded by the investigator and sponsor. For assessment of causality, the IB and the risk analysis report will be consulted. The sponsor and investigator will distinguish between SAEs related to the investigational device and those related to the procedures, relatedness to both is possible.
Each SAE will be classified according to four different levels of causality:

1. Not related
   Relationship to the device, comparator or procedures can be excluded when:
   - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
   - the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
   - the event involves a body-site or an organ that cannot be affected by the device or procedure;
   - the SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

2. Possible
The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained shall also be classified as possible.

3. Probable
The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship
The SAE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

14.3 List of foreseeable Adverse events

Foreseeable adverse events*	Incidence (%)	Mitigation and treatment
Adverse events		
Sore throat	44	Conservative treatment, analgesics
Dyspepsia indigestion reflux	13	Conservative treatment, acid suppressants
Oesophageal or gastric pain	11	Conservative treatment, analgesics

Feeling non-specifically unwell	6	Conservative treatment
Nausea or vomiting	6	Conservative treatment, antiemetics
Voice disturbance	3	Conservative treatment
Diarrhea or an upset stomach	4	
Chest pain or discomfort	1	Conservative treatment, analgesics
Allergic reaction	1	Conservative treatment, allergy treatment
Anxiety	1	Conservative treatment
Bad taste	1	Conservative treatment
Paroxysmal positional vertigo	1	Conservative treatment
Blood clot excretion	1	Conservative treatment
Vasovagal attack	1	Conservative treatment
Nosebleed	1	Conservative treatment
Headache	1	Conservative treatment, analgesics
Bloodshot eye	1	Conservative treatment
Chest infection	1	Conservative treatment, antibiotics
Abrasion	1	Conservative treatment
Fall	1	Conservative treatment, orthopedic consultation
Serious adverse event		
Detachment of the sponge on day of the procedure	1	Endoscopy
Hernia	1	Surgery
Myocardial infarction	1	Cardiological treatment
Perforation	N/A	Endoscopic or surgical intervention, conservative treatment, antibiotics
Serious bleeding	N/A	Endoscopic or surgical intervention, blood transfusions

15 Premature termination of the clinical investigation

The sponsor may suspend or prematurely terminate either the clinical investigation at an individual investigation site or the entire clinical investigation for significant and documented reasons. The Swedish Medical Products Agency may suspend or prematurely terminate the clinical investigation at the applicable investigation sites.
If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the Medical Products Agency, the sponsor will suspend the clinical investigation while the risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. The sponsor will inform all investigators.
The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.
If, in the opinion of the investigator, the clinical observations in the clinical investigation suggest that it may be unsafe to continue the investigation at the site, the investigator may terminate participation in the investigation after consultation with the sponsor. A written statement fully documenting the reasons for such termination will be provided to the sponsor.
If the clinical investigation is prematurely terminated, the investigators shall promptly inform the subjects and take necessary steps to finalize their engagement in the clinical investigation. All relevant investigation material must be collected, and accountability completed.
If the clinical investigation is interrupted or terminated prematurely the sponsor will report to the Medical Products Agency within 15 days together with a justification. If the sponsor has temporarily halted or prematurely terminated the clinical investigation on safety grounds, the Medical Products Agency will be informed within 24 hours. A clinical investigation report will be prepared within three months of the early termination or temporary halt, irrespective of the results. In the event that the clinical investigation is restarted within three months of the temporary halt, the sponsor does not have to submit a clinical investigation report until the clinical investigation has been completed.

The final clinical investigation report shall include detail with respect to the temporary halt.

16 Publication policy

The clinical investigation will be registered in a publicly accessible database before the start of recruitment activities and the content will be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation. The results will be presented at national and international scientific meetings and published in scientific journals.

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18 Appendix

Appendix A – EndoSign® Cell collection device -_Instructions for use
Version No: 1.1
Date: 2023-11-29