STUDY TITLE:

ENDOSCOPIC SUBMUCOSAL DISSECTION USING GEL VERSUS GLYCEROL FOR SUBMUCOSAL INJECTION: A RANDOMIZED CONTROLLED MULTICENTRIC TRIAL (EPSILON)

NCT NUMBER: NOT YET ASSIGNED

ENDOSCOPIC SUBMUCOSAL DISSECTION USING GEL VERSUS GLYCEROL FOR SUBMUCOSAL INJECTION: A RANDOMIZED CONTROLLED MULTICENTRIC TRIAL (EPSILON)

Version no 1.12 – 21/07/2021

Study Type:	Prospective, open-label, randomized (1:1), multicentric academic study
Study Registration:	EPSILON
Sponsor-Investigator:	Arnaud LEMMERS, MD, PhD Department of Gastroenterology, Hepatopancreatology and Digestive Oncology Erasme Hospital Route de Lennik, 808 - B-1070 Brussels, Belgium +32 2 555 6559 –T +32 2 555 37 12- F +32 (0) 2 555 46 97 Arnaud.Lemmers@erasme.ulb.ac.be
Local Investigators/ Subinvestigators:	***Erasme Hospital (Brussels, Belgium):*** Vincent Huberty, MD, PhD Ana-Maria BUCALAU, MD ***Keio Cancer Center (Tokyo, Japan):*** Naohisa Yahagi, MD, PhD Motohiko Kato, MD, PhD Matsura Noriko, MD ***Eveangelisches Krankenhaus, Teaching Hospital of Dusseldorf (Germany)*** Torsten Beyna, MD, PhD Horst Neuhaus, MD, PhD ***Memorial Sloan Kettering Cancer Center , NYC (USA)*** Makoto Nishimura, MD Dr Leung, MD
Investigational Product:	Orise™ gel
Protocol Version and Date:	Version 1, dated 21st of July 2021

Trial management and coordinating facility:	Clinical research unit Department of Gastroenterology, Hepatopancreatology and Digestive Oncology CUB Hôpital Erasme Route de Lennik 808 B – 1070 BRUXELLES Tel: +32 2 555 3016 / 4764 Fax: +32 2 555 8236

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CLINICAL STUDY PROTOCOL INVESTIGATOR SIGNATURE PAGE

Study reference:	EPSILON
Study Title:	***EndoscoPic Submucosal dIssection using geL versus glycerOl for submucosal iNjection: a randomized controlled multicentric trial (EPSILON)***

The Sponsor-Investigator has approved the protocol version dated and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines, ISO 14155 norm and the local legally applicable requirements.

Sponsor-Investigator:

Arnaud LEMMERS, MD, PhD
Department of Gastroenterology, Hepatopancreatology and Digestive Oncology
Erasme Hospital
Route de Lennik, 808 - B-1070 Brussels, Belgium

Date Signature

1. Protocol synopsis

Name of Finished Product/device: Orise™ gel	
Title of Study: ***EndoscoPic Submucosal dIssection using geL versus glycerOl for submucosal iNjection: a randomized controlled multicentric trial (EPSILON)***	
Indication: Endoscopic resection by ESD of gastric and rectal superficial lesions	
Study centers: **Erasme University Hospital** Department of Gastroenterology, Hepatopancreatology and Digestive Oncology Route de Lennik, 808, 1070 Brussels, Belgium **Eveangelisches Krankenhaus, Teaching Hospital of Dusseldorf**, Department of Internal Medicine Kirchfeldstraße 40, 40217 Düsseldorf, Germany **Cancer Center, Keio University School of Medicine** Division of Research and Development for Minimally Invasive Treatment 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582 Japan **Memorial Sloan Kettering Cancer Center** 1275 York Avenue, New York, NY 10065	
Number on participating Belgian Centers	1
Number of participating international centers	3
Studied period (years): Q2 2021-Q2 2024	**Clinical Phase:** Prospective, open-label, randomized (1:1), multicentric academic study
Hypotheses: Submucosal injection of ORISE™ gel will shorten ESD procedure duration by improving lesion lifting and reducing the number of per-procedural bleedings.	

Study Design:

A multicentric, randomized, open label prospective study:

- All subjects with indications of gastric and rectal ESD undergo screening and baseline visit
- Informed consent is obtained when scheduling the ESD procedure
- Randomization is made at the time of the ESD procedure after confirmation of the indication
- ESD is performed using a 25 G needle, a dual-knife-J with glycerol (standard solution) or ORISE^{TM} gel in order to remove the lesion en-bloc. Additional saline injection through the electrosurgical knife will be left at the discretion of the endoscopist
- A follow-up visit is scheduled at 2-4 weeks

Study visits:

- Screening and baseline
- ESD procedure
- Post-treatment follow-up at 2_4 weeks

Number of patients (planned and analyzed): 133 patients by arm with a total of 266

Endpoints :

- Primary:

  - Increase the dissection speed of the ESD procedure (defined as the dissected surface (mm2)/ESD duration (min). The dissected surface is defined as maximal diameter of specimen (mm) x perpendicular minimal diameter of specimen (mm) measured on ex-vivo pinned stretched specimen onto a cork. ESD duration is defined as the time from first submucosal injection to final cut time.

- Secondary:

  - Total procedure duration (from scope insertion to scope retrieval) (min)
  - Number of per-procedural bleeding (+ severity scale: oozing / severe non pulsating/ severe pulsating)
  - total hemostatic time (addition of each hemostasis time for each per-procedural bleeding)
  - Need for haemostatic forceps during ESD
  - Difficulty of the dissection (scale)
  - Amount of submucosal solution (glycerol or gel) used for ESD in ml
  - Combined use of saline through the knife during ESD (number and ml)
  - Number of needle injection dots during ESD (initially / during ESD)
  - Need to adjust electrosurgical settings during ESD
  - Clear visualisation of the plane of dissection during ESD (scale) (defined in the protocole)
  - Rate of en-bloc dissection (defined as endoscopic resection of the targeted area in one bloc)
  - Rate of complete endoscopic resection (defined as endoscopic evaluation of complete removal of the targeted area in the treated organ)
  - Quality assessment of the pathological specimen (absolute measure of the depth of resected submucosa on the specimen, rate of clear (horizontal and vertical) margins)

- Adverse events:
  - Per-procedural (incidence of all adverse technical events during the procedure)
  - Early (clinical and laboratory at 24 h post procedure according to CTCAE v 5.0)
  - Late (clinical at 3 weeks follow-up)

Main criteria for inclusion and exclusion:

- Inclusion:
  - Subject ≥18 years of age at the time of informed consent
  - Patients must have given written informed consent
  - Subjects with documented gastric or rectal lesions with indication of endoscopic removal by ESD, namely:
    - Gastric focal lesion with suspicion of early gastric cancer (low or high grade dysplasia with features of early gastric cancer; adenocarcinoma with morphology of superficial lesion and work-up of superficial lesion)
    - Rectal polyps (adenoma or superficial carcinoma) from 0 to 15 cm from the anal margin; with features being recognized indications of ESD: more than 20mm granular LST, more than 20mm non granular LST, more than 20mm villous or bulging polyps, Paris 0-IIa+IIc lesions, lesions with suspicious pattern (Kudo Vi / JNET 2B), lesions with anal canal involvement.
- Exclusion:
  - Subjects who meet any of the following exclusion criteria cannot be enrolled in the study:
    - Gastric and rectal neuroendocrine tumour (NET) with indication of ESD will be excluded
    - Gastric and rectal lesions with indication of ESD but strong fibrosis due to previous partial resection will be excluded
    - Subject is currently enrolled in another confounding research
    - Subjects with any other location of ESD (esophagus, duodenum and colon) will not be included.

Support request: Glycerol or ORISE^{TM} gel will be ordered as other pharmaceuticals by the hospital and billed as locally done in routine practice. A collaborative research agreement between Boston Scientific and Erasme Hospital will be signed.

Procedures: Schedule of assessments in Table 1

Statistical Considerations: Sample size was computed using a two-sided Welch T-Test (groups with unequal variances) using an $\alpha = 0.05$ and a power of 80%.

2. Table of contents

3. Ethics

Study registration
The study will be registered on ClinicalTrial.gov.

Categorization of study
We aim to conduct a prospective randomized, open-label, multicentric academic study comparing endoscopic submucosal dissection (ESD) using ORISE^{TM} gel versus glycerol for submucosal injection. A cooperative research agreement between Erasme hospital (Brussels) and Boston Scientific will be signed.
The Orise^{TM} gel solution has obtained a CE mark on the 13th of November 2018, and is FDA approved. Its intended use remains unchanged as it was registered to use as a submucosal lifting solution for endoscopic resection.
Orise^{TM} gel is a premixed sterile solution, prepared in syringes of 12ml, of gum solubilized in saline and calcium chloride with alimentary blue dye.
Glyceol is a premixed commercially available sterile solution containing 10% glycerol, 5% fructose in saline. Blue Indigo dye is manually added to obtain light blue colour.

Competent Ethics Committee (CEC)
This protocol, any protocol amendments, and other relevant documents are submitted to the Ethics Committee of Erasme Hospital (Brussels), Eveangelisches Krankenhaus hospital (Dusseldorf), Memorial Kettering Sloan Cancer Center (New York City) and Keio Cancer Center (Tokyo) for formal approval to conduct the study. No changes will be made to the protocol without prior CEC approval. Premature study end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CEC within 90 days, the final study report will be submitted within one year after study end.

Ethical conduct of the study
The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP). The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

Declaration of interests
There is no intellectual, financial or proprietary conflict of interest to declare by the principal investigator or the co-investigators.

Patient Information and Informed Consent
The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.
The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The choice will be given to the participant to decide whether to participate.
The patient information sheet and the consent form will be submitted to the CEC and to the competent authority to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.
The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

Participant privacy and confidentiality
The investigators affirm and uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.
For data verification purposes, authorised representatives of the investigator, a competent authority or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

Early termination of the study
The Sponsor-Investigator, the competent authority or the competent ethics committee may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

In the case of an early termination, the sponsor-investigator will notify the end of the trial to the National Competent Authority of the Member State concerned (FAMHP) immediately and at least within 15 days from when the trial is halted, and clearly explain the reasons. "Premature end" is considered as "early termination".

Declaration of end of trial
End of trial is defined as follows: the date of the last visit of the last patient undergoing the trial. Within 90 days of the end of a clinical trial, the sponsor-investigator shall notify the competent authorities of the Member State (FAMHP) and the Ethics Committee that the clinical trial has ended.

The sponsor-investigator will make an end of trial declaration using the form published in Volume 10 of Eudralex – the Rules Governing Medicinal Products in the European Union. http://ec.europa.eu/health/files/eudralex/vol-10/declaration_end_trial_form.doc

4. Background and rationale

Superficial gastrointestinal (GI) cancers are defined as lesions limited to the mucosa or submucosa without invading the muscularis propria. With the spread and improvement of the quality of endoscopy, early detection of GI cancers or precancerous lesions is growing. Endoscopic resection has been shown to be an adequate treatment for patients with early GI cancers with no or limited submucosal involvement and no additional risk factors. Most superficial lesions may be treated by endoscopic mucosal resection (EMR), such as subpenduculated/pedunculated and small flat lesions [1]. However, this technique is unsuitable for en-bloc resection of lesions larger than 15-20 mm or of non-lifting lesions, as it does not permit adequate histological examination of early cancers. To overcome these limitations, endoscopic submucosal dissection (ESD) has been developed. Firstly described in Japan more than 15 years ago, ESD is progressively gaining more attention in Western countries. The basic technique of ESD involves three steps: injection of fluid into the submucosa to elevate the lesions from the muscle layer, pre-cutting the surrounding mucosa of the lesion and dissection the connective tissue of the submucosa beneath the lesions(Figure 1)[2]. The advantage of ESD over classical mucosectomy is the possibility to remove en-bloc the whole lesion without limits due to the size or poor lifting in case of fibrosis. This leads to improved pathological specimen quality without risk of misinterpretation, such as in the case of positive lateral margins for piece-meal resection, avoiding unnecessary surgery. Furthermore, recurrence rate has been demonstrated in several situations (early gastric cancer, squamous cell carcinoma, colorectal adenoma) to be lower when removing a preneoplastic / early cancerous lesion en-bloc with clear margins compared to piece-meal resection[3,4,5]. Currently, a niche for selected GI superficial lesions (larger than 15-20 mm, suspected of submucosal invasion or fibrotic content) to be treated by ESD has been proposed by the European Society of Gastrointestinal Endoscopy (ESGE) guidelines[6].

Different techniques and instruments have been developed in order to facilitate this otherwise challenging procedure. Traditionally, ESD requires the injection of some colloidal solution (glycerol, geloplasma, hydroxyethylstrach, etc.) in the submucosal layer in order to obtain long lifting effect and thus allowing the endoscopist to dissect under the lesion[7,8]. Over the past 5 years, the injection technique has improved due to the developement of jet-knifes, allowing to add submucosal lifting agent through the knife, thus diminishing the duration of the procedure by evoiding instrument change via the operating channel. Alternatives to colloid-solution assisted ESD have also been developped: pocket creation method and saline-immersion ESD[9,10]. These techniques use saline injection as a lifting agent and make use of the favorable effect of buoyancy, which helps counteract the force of gravity, creating a traction effect, which is particularly useful in the context of fibrosis.

Furthermore saline maintains a thick, fluid-soaked submucosa, reducing the requirement for submucosal injection of lifting solution.

Although described to be more easy and quick, several drawbacks of these two ESD techniques have been described, such as the difficulty to open the pocket at the end of the resection, need to come with the tip of the scope in and out of the pocket to understand the limits of the needed dissection area and need of clear vision under the saline, with troubles in case of per-procedural bleeding.

Recently, other colloidal solutions have arrived on the market, such as gel (ORISE^{TM} gel) in order to improve the lifting during ESD. Our preliminary experience using ORISE^{TM} gel as a lifting solution for ESD was unexpectedly favourable with few per-procedural bleeding (possibly due to the viscosity of the fluid taking more space in the submucosa and reducing blood supply in capillaries during the ESD), quick time and facility. As the spread of ESD is closely associated to its easiness, procedure duration (itself associated to number of procedural bleedings and instruments change through the operating channel) and safety, we sought to study comparatively two submucosal solutions when conducting ESD in a specific population presenting gastric or rectal superficial lesions.

5. Study objectives and endpoints

5.1. Study objectives

The EPSILON study aims to comparatively evaluate the submucosal injection using ORISE^{TM} gel and glycerol during an ESD procedure in a specific population with superficial gastric and rectal (pre)neoplastic lesions.

5.2. Study endpoints

5.2.1. Primary

- Increase the dissection speed of the ESD procedure (defined as the dissected surface (mm2)/ESD duration (min). The dissected surface is defined as maximal diameter of specimen (mm) x perpendicular minimal diameter of specimen (mm) measured on ex-vivo pinned stretched specimen onto a cork. ESD duration is defined as the time from first submucosal injection to final cut time.

5.2.2. Secondary

- Total procedure duration (from scope insertion to scope retrieval) (min)
- Number of per-procedural bleeding (+ severity scale: oozing / severe non pulsating/ severe pulsating)
- Total hemostatic time (addition of each hemostasis time for each per-procedural bleeding)

- Need for haemostatic forceps during ESD
- Difficulty of the dissection (scale)
- Amount of submucosal solution (glycerol or gel) used for ESD in ml
- Combined use of saline through the knife during ESD (number and ml)
- Number of needle injection dots during ESD (initially / during ESD)
- Need to adjust electrosurgical settings during ESD
- Clear visualisation of the plane of dissection during ESD (scale). The scale will be defined according the endoscopists evaluation of the delineation between the submucosa ad the underlying muscular layer:
    - Very-good visualization: clear delineation between the two layers with clear visualization of the blood vessels.
    - Good visualization: mostly clear delineation between the two layers, but with blurred regions
    - Bad visualization: delineation between the two layers is unclear (i.e.: fibrosis)
- Rate of en-bloc dissection (defined as endoscopic resection of the targeted area in one bloc)
- Rate of complete endoscopic resection (defined as endoscopic evaluation of complete removal of the targeted area in the treated organ)
- Quality assessment of the pathological specimen (absolute measure of the depth of resected submucosa on the specimen, rate of clear (horizontal and vertical) margins)
- Adverse events:
    - Per-procedural (incidence of all adverse technical events during the procedure)
    - Early (clinical and laboratory at 24 h post procedure according to CTCAE v 5.0)
    - Late (clinical at 2-3 weeks follow-up)

6. Study design

6.1. Study design

We aim to conduct an multicentric, open label, prospective randomized (1 :1) academic study comparing the submucosal injection using ORISE^{TM} gel and glycerol in a specific population with superficial GI (pre)neoplastic lesions (see Schedule of assessments in Table 1). Patients will be referred by their gastroenterologist after index gastroscopy/colonoscopy showing a potential superficial (pre)neoplastic lesion.

6.2. Sample size and randomization

Based on available data of the dissection speed from Erasme, we calculated the dissection speed using the Orise gel and glycerol. These means and standard deviations are shown in the table below.

	Group Glyceol		Group Gel ORISE		Delta Speed (Gel - Glyceol)	
center	n	Speed (mm^2/min)	n	Speed (mm^2/min)	Speed (mm^2/min)	% of increase
Erasme	31	17.11 ± 18.27	10	22.24 ± 10.26	5.13 ± 4.61	**23.06 %**

A power analysis was performed using the results above to calculate the sample size. Using a two-sided Welch T-Test (groups with unequal variances) with an $\alpha = 0.05$ and power of 80%, with 1:1 randomization, 133 patients would be required to show a statistically significant difference between the groups. If this hypothesized difference is proven this would be a 23% increase in the speed of dissection. The results will also be stratified by site to see if any differences are observed, this will be performed using a generalized linear model.

A computer-based block randomization scheme will be created using block randomization and stratifying by center and by organ type (stomach/rectum). Data will be collected through a printed CRFs and then anonymized and entered into a central web based secured platform.

6.3. Participating centres

Four centres will participate in this study:
- CUB Hôpital Erasme, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology from Belgium
- The Teaching Hospital of Dusseldorf, Department of Gastroenterology, Eveangelisches Krankenhaus from Germany.
- Cancer Center, Keio University School of Medicine, Division of Research and Development for Minimally Invasive Treatment, Tokyo, Japan.
- Memorial Sloan Kettering Cancer Center, New York, USA

6.4. Study duration

Enrolment will begin Q2 2021 until Q2 2024, taking in account a follow-up of 3 weeks for each patient in order to evaluate the possible late adverse events.

6.5. Study periods

The study will comprise 3 periods:
- Day -15 to Day -1: The screening period will precede the randomized procedure.
- Day 0-1 : Treatment (ESD) Period (randomization and treatment)
- Week 1 to Week 2-4: follow-up.

6.6. Screening period (Day -15 to day -1)

The following screening procedures will be performed for all potential patients at the screening conducted during the screening period and prior to randomization:

- If possible, High-definition gastroscopy/rectoscopy for lesion evaluation (using chromoendoscopy and near-focus)
- Signature of informed consent witnessed by the Investigator or designated person.
- Patient randomization number allocation.
- Check medical history/demographics.
- Check inclusion/exclusion criteria
- Physical examination
- Check concomitant/prior medication (within 1 month prior to Screening)

6.7. Treatment period (Day 0-1)

- Procedure (Day 0): photo documentation of the lesion, ESD procedure, photo documentation of the specimen and resection field.
- Day 0 to +1 : clinical and biological follow-up and discharge (i.e. if no adverse effect is observed). Duration of hospital stay for subjects post procedure is determined by local healthcare practice and healthcare system guidelines and is left at the investigator's discretion.

6.8. Follow-up

- Clinical follow-up will be performed at Week 2-4 during outpatient visit or by phone call ; check AEs and occurrence of any clinical outcome

6.9. Follow-up for patients who have permanently discontinued the study

If a subject discontinues participation in the study, he or she will be contacted to obtain information about the reason(s) for discontinuation and collection of any potential Aes. The Investigator will document the reason for Subject Withdrawal on the Patient Case Report Form (CRF). Discontinued patients will be followed until all Aes resolve or until the Investigator decides that follow-up are no longer needed.

7. Patient selection

7.1. Inclusion criteria

- Subject ≥18 years of age at the time of informed consent
- Patients must have given written informed consent
- Subjects with documented gastric or rectal lesions with indication of endoscopic removal by ESD, namely:
    - Gastric focal lesion with suspicion of early gastric cancer (low or high grade dysplasia with features of early gastric cancer; adenocarcinoma with morphology of superficial lesion and work-up of superficial lesion)
    - Rectal polyps (adenoma or superficial carcinoma) from 0 to 15 cm from the anal margin; with features being recognized indications of ESD: more than 20mm granular LST, more than 20mm non granular LST, more than 20mm villous or bulging polyps, Paris 0-IIa+IIc lesions, lesions with suspicious pattern (Kudo Vi / JNET 2B), lesions with anal canal involvement.

7.2. Exclusion criteria

- Subjects who meet any of the following exclusion criteria cannot be enrolled in the study:
    - Gastric and rectal neuroendocrine tumour (NET) with indication of ESD will be excluded
    - Gastric and rectal lesions with indication of ESD but strong fibrosis due to previous partial resection will be excluded
    - Subject is currently enrolled in another confounding research
    - Subjects with any other location of ESD (esophagus, duodenum and colon) will not be included.

8. Study procedure

8.1. Screening endoscopy

Patients will be addressed for ESD by their gastroenterologist after index gastroscopy/colonoscopy showing a potential superficial (pre)neoplastic lesion. A “second look” endoscopy before being admitted for ESD remains at the discretion of the endoscopist. Further investigations by EUS, pelvic MRI or/and chest and abdominal CT scan will be recommended depending on the endoscopic evaluation and center oncological consensus management.

8.2. ESD procedure

First, the lesion will be closely inspected by high-resolution endoscopy with white light and narrow banding imaging (NBI) with near focus (GIF-HQ190 Olympus Medical System, Tokyo, Japan). Size, shape (Paris classification, LST classification for rectum), endoscopic features (NICE and JNET classification) and location will be reported[11–13].

The ESD procedures will be performed under general anesthesia with orotracheal intubation or under sedation following center experience. Carbon dioxide will be used used for insufflation.
Using an HQ 190 Olympus gastroscope (EXERA III) or 290 series (LUCERA) in Japan or 1500EZ using Evis X1), fitted with a transparent cap at its end (D-206 or equivalent; Olympus), the gastric lesions will delimitated and marked by the ESD knife tip (i.e Dual-(J) Knife (Olympus Medical Systems, Tokyo, Japan), with soft coagulation mode (VIO 300 Effect 5, 50 watts; VI03 E 5.5). Marking dots are not required for rectal lesions due to their clear delineation from the normal mucosa.
According to randomization, using a 25G needle, the lesion will be lifted with a Glyceol solution with indigo blue dye or ORISE™ gel. Mucosal incision will be performed using Dry Cut mode, (E3 30 watts Erbe VIO 300D, E 3.5 Erbe VIO 3; Tubingen, Germany) and subsequent submucosal dissection using dry cut or swift coagulation mode, (VIO 300 E4 30watts; VIO3 E3.5). After mucosal opening, further lifting during the ESD will be performed using the needle or the tip of the knife pushed into the submucosal space with the Glyceol or ORISE™ gel according to randomization. Added saline injected though the tip of the knife is allowed in both groups (with recorded volume) according to the endoscopists convenience. Visible vessels and bleedings will be coagulated with the knife tip (slowly using swift coag E4 30W or using Forced coag E1 15W) or a 4mm (rectum) or 5mm (stomach) coagulation forceps (Coagrasper, Olympus), using soft coagulation (VIO 300 Effect 5, 50 watts (rectum) / 80 watts (stomach); VIO3 E 5.5). For gastric ESD, 80mg of Intravenous PPI will be given during the procedure and 12h later; at discharge PPI 40mg BID will be given after gastric ESD. After the resection, the specimen will be pinned on a cork (or equivalent) to stretch it moderately and expose the lateral margins. Then, measures of the maximal diameter (mm) and perpendicular minimal diameter will be obtained and recorded by picture capture using the scope. Thereafter, it will be immerged into formaldehyde and sent to the pathologic lab.

Patients will remain hospitalized overnight and a blood test will be performed before their discharge.

9. Assessments per procedure

- Duration of ESD procedure defined as the time of first injection to final cut time
- Total duration of the endoscopic procedure (from endoscope insertion to scope retrieval)
- Calculated speed of the dissection (surface dissected (mm^2)/ESD duration (min)).
- Number of per-procedural bleeding (+ severity scale: oozing / severe non pulsating/ severe pulsating)
- Total hemostatic time (addition of each hemostasis time for each per-procedural bleeding)
- Need for haemostatic forceps during ESD
- Difficulty of the dissection (scale)
- Amount of submucosal solution (glycerol or gel) used for ESD in ml

- Combined use of saline through the knife during ESD (number and ml)
- Number of needle injection dots during ESD (initially / during ESD)
- Need to adjust electrosurgical settings during ESD
- Clear visualisation of the plane of dissection during ESD (scale)
- Rate of en-bloc dissection
- Rate of endoscopic complete resection
- Quality assessment of the pathological specimen
- Adverse events:
    - Per-procedural (incidence of all adverse technical events during the procedure)

10. Adverse event

10.1. Reporting of adverse events (AE), serious adverse events (SAE), serious adverse device effects (SADE), unanticipated serious adverse device effects (USADE)

All adverse events (AE), serious adverse events (SAE), Serious Adverse Device Effects (SADE), Unanticipated serious adverse device effects (USADE) will be collected and documented in the source documents and appropriate case report forms (CRF) during the entire study period, i.e. from patient's informed consent until the last protocol-specific procedure, including a safety follow-up period. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure.

10.2. Definition and assessment of (serious) adverse events and other safety related events

10.2.1. Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational device or the comparator. NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical device.

10.2.2. Serious Adverse Event (SAE)

Adverse event that:

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

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

10.2.3. Device deficiency

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

10.2.4. Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

10.2.5. Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

10.2.6. Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

10.3. Causality assessment

The relationship between the use of the medical device 13 (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. During causality assessment activity, clinical judgement shall be used and the relevant

documents, such as the Investigator's Brochure, the Clinical Protocol or the risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. The above considerations apply also to the serious adverse events occurring in the comparison group. For the purpose of harmonising reports, each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures.

1. Not related: relationship to the device or procedures can be excluded when:
    - ✓ the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
    - ✓ the event has no temporal relationship with the use of the investigational device or the procedures;
    - ✓ the serious event 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 event;
    - ✓ the event involves a body-site or an organ not expected to be affected by the device or procedure;
    - ✓ the serious event 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;
    - ✓ harms to the subject are not clearly due to use error;
    - ✓ 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 serious event.

2. 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.
3. Possible: the relationship with the use of the investigational device 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 were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
4. Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
5. Causal relationship: the serious event is associated with the investigational device 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
- ✓ o the investigational device or procedures are applied to;
- ✓ o the investigational device or procedures have an effect on;
- ✓ the serious 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 serious event (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 serious event

The following events will be reported by the sponsor-investigator to the Competent Authorities **(meddev@fagg.be):**

- any SAE
- any Device Deficiency 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
- any new findings/updates in relation to already reported events.

by using the European Form:
https://www.fagg-afmps.be/sites/default/files/downloads/sae_reporting_form_en.xlsx

10.4. Reporting timelines

The sponsor-investigator will report to the National Competent Authority where the clinical investigation has commenced:

- all reportable events as described above which 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: 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 as described above or a new finding/update to it: 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.

10.5. Periodic safety reporting

A yearly safety update-report will be submitted by the Sponsor-investigator to the Ethics Committee.

11. Financing and insurance

This is an academic investigator initiated study. All enrolled patients will have an insurance coverage from the risks derived from their participation to this study.

12. References

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13. Appendix – figures and tables

Figure 1- ESD procedure

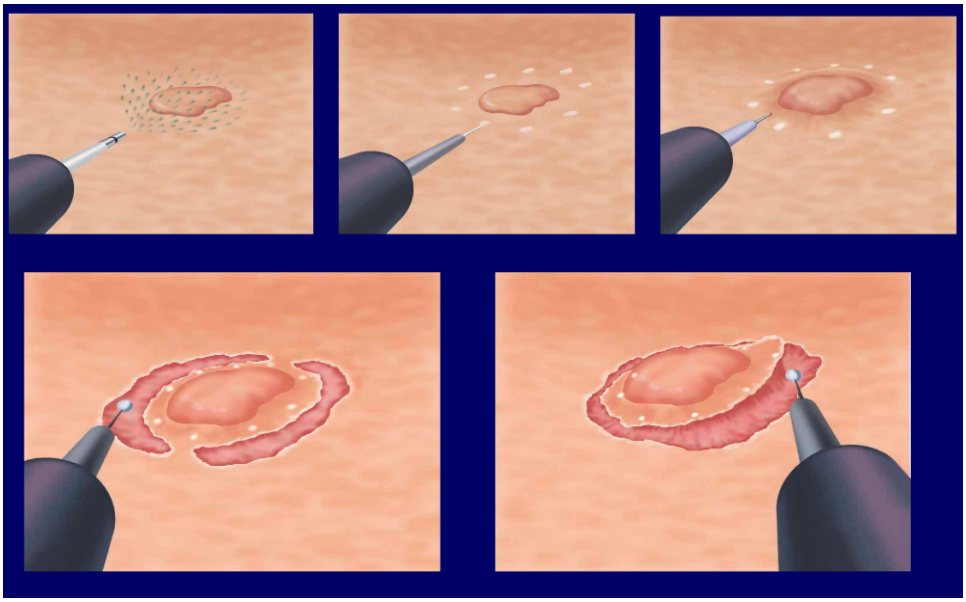

Table 1- Schedule of assessments

	Baseline	D-15 to D-1	D0	D+1	Week 2-4
Signature of informed consent	X				
Randomization			X		
ESD procedure			X		
AEs evaluation			X	X	X