Statistical Analysis Plan

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

EPSILON

NCT number : not yet assigned

Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change

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1 PROTOCOL SUMMARY

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): Q4 2020-Q4 2023	**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™ 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 INTRODUCTION

This statistical plan addresses the planned analyses for the study on the EPSILON on the protocol dated November 9, 2020. Specified analyses may be used for scientific presentation and/or manuscripts and may not all be provided to Competent Authorities.

3 ENDPOINT ANALYSIS

3.1 Primary Endpoint

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.

3.1.1 Hypotheses

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.

4 ADDITIONAL DATA ANALYSES

4.1 Secondary Endpoints

- 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)

1) Evaluation of serious adverse events (SAEs) related to the device and/or the procedure through 30 days after the ERCP.

4.2 Baseline Data

Subject demographics and clinical history will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency statistics for discrete variables.

4.3 Procedure Data

Procedure data including qualitative evaluation will be collected and reported using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency statistics for discrete variables.

4.4 Post-Procedure Data

Post-procedure information will be collected as detailed in the **Erreur ! Source du renvoi introuvable.** of the protocol. Data Schedule and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency statistics for discrete variables.

4.5 Interim Analyses

No formal interim analyses are planned for this study.

4.6 Subgroup Analyses

Stratified analyses will include tabulating the primary and select secondary endpoints by gender.

4.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses.

5 PROGRAMMING CONSIDERATIONS

5.1 Rules and Definitions

- Binary event rates (proportions) will be reported on a per-patient basis.
- The last follow-up date will be the latest of the following dates for each patient: date of an adverse event, procedure date, follow-up visit date, and device event date.
- Serious Adverse Event will be defined as an adverse event that:
    - Led to death
    - Led to a serious deterioration in the health of the subject that either resulted in:
        - a life-threatening illness or injury, or
        - a permanent impairment of a body structure or a body function, or
        - in-patient hospitalization or prolonged hospitalization (of an existing hospitalization), or
        - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
    - Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
- When calculating rates of adverse events, missing and partial dates will be handled as follows:

Partial Date Description	**Action Taken**
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1 will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.