Suprasorb® CNP endo used for negative pressure therapy in the oesophagus and rectum to support defect and wound healing

Study Protocol

Title	Suprasorb® CNP endo used for negative pressure therapy in the oesophagus and rectum to support defect and wound healing
Short title/ acronym	Velox Study
Protocol version identifier	Version no. 1.0 dated 07.12.2023
Study register number	NCT05476263
Type of study	This PMCF study designed as non-interventional, observational, prospective, multicentre study in a routine clinical care setting using a marketed medical device in line with the corresponding IFU in the intended patient population.
Country(ies) in the study	Germany
Most relevant regulatory standards to be followed	ISO 14155:2020, EU MDR (as far as applicable), GDPR, Medizinprodukte-Anwendermelde- und Informationsverordnung (MPAMIV)
Legal Sponsor	Lohmann & Rauscher GmbH & Co. KG Irlicherstr. 55, 56567 Neuwied, Germany
CRO	CRI – The Clinical Research Institute GmbH Arnulfstr. 19, 80335 Munich, Germany
Medicinal product of interest	Suprasorb® CNP endo
Medicinal Product Marketing Authorisation No.	Suprasorb® CNP endo therapy unit Basic UDI-DI No. 426058604EndoAspE2, dated 16.06.2021; CNP endo Foam Drain CE certificate No. G10 045286 0079 Rev 01, dated 03.08.2023; CNP endo Foam Drain N CE certificate No. G10 045286 0079 Rev 01, dated 03.08.2023; CNP endo Overtube Basic UDI-DI No. 4021447-0181-L4, dated 29.08.2023; CNP endo Proctoscope Basic UDI-DI No. 37016034AUP24A5, dated 10.11.2022; CNP endo Nasal Tube Basic UDI-DI No. 4021447-0180-KZ, dated 29.08.2023; CNP endo Tube Clamp Basic UDI-DI No. 4021447-0184-LD, dated 29.08.2023; CNP endo Y-Connector Basic UDI-DI No. 4021447-0185-LG, dated 29.08.2023; CNP endo Nasal Dressing Basic UDI-DI No. 4260402642375H, dated 27.05.2021; CNP endo Rectal Fixation Dressing REF No. 90-30-14, dated 27.05.2022;
Marketing authorisation holder(s)	Lohmann & Rauscher International GmbH & Co. KG Westerwaldstr. 4, 56579 Rengsdorf, Germany
Author of protocol	Thomas Fetsch, MD (CRI), Daria Trofimenko, MD (Lohmann & Rauscher)

All information in this study protocol including attachments provided to you as investigator, potential investigator, sub-investigator, committee member or other third party must be treated confidentially. The right to use this information is limited to you, your staff, members of the relevant committees or entitled authorities. The objectives and the content of this study, as well as its results, must be treated confidentially and may not be made available to third parties at any time before, during and after the study without written approval of the sponsor except to the extent necessary to get informed consent from patients. This applies to investigators and all supporting staff involved in the study. Transmission, duplication or use for publication is permitted only with the written agreement of the sponsor.

Table of contents

List of abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AEoSI	Adverse Event of Special Interest
CAL	Colorectal Anastomotic Leakage
CEC	Clinical Event Committee
CFR 11	Code of Federal Regulations Part 11 (USA)
CDISC	Clinical Data Interchange Standards Consortium
CRO	Contract Research Organisation
CTMS	Clinical Trial Management System
e-CRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
EVAC	Endoscopic Vacuum-Assisted Closure
EVT	Endoscopic / Endoluminal Vacuum Therapy
FPI	First Patient In
FU	Follow-up
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH-GCP	International Conference on Harmonisation on Good Clinical Practice
ICU	Intensive Care Unit
IFU	Approved Instruction For Use of a medical device according to CE certification
ITT	Intention-To-Treat
LOS	Length of stay
LPI	Last Patient In
LPO	Last Patient Out
MDR	EU Medical Device Regulation 2017/745
OTSC	Over-The-Scope-Clip
PMCF	Post-Market Clinical Follow-up as defined in EU MDR, especially Annex XIV
PRRC-V	Person Responsible for Regulatory Compliance-Vigilance
PSS	Perforation Severity Score
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SEMS	Self-Expanding Metal Stent
SEPS	Self-Expanding Plastic Stent
SOP	Standard Operating Procedure

Signatures

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with applicable regulations.

Date	Signature
_____	_____ Dr Maria Burian, SC member
_____	_____ Dr Marcus Kantowski, SC member
_____	_____ Dr Konstantinos Kouladouros, SC member
_____	_____ Prof Dr Mike Laukötter, Chair of SC
_____	_____ Dr Gunnar Loske, SC member
_____	_____ Prof Dr Anja Schaible, SC member
_____	_____ Dr Christine Stier, SC member
_____	_____ Dr Martin Abel, Sponsor representative

_____	_____ Signature of principal investigator of study site
	_____ Name of principal investigator of study site

1. General

This study protocol reflects the topics defined in annex A (clinical investigation plan) of ISO 14155:2020. Topics 1.1 to 1.3 are represented on the cover page, thus, numbering starts with topic 1.4 of annex A as 1.1 of this study protocol. Some headlines of annex A have been modified to better represent the needs of this non-interventional, observational study, e.g. 1.4 (here 1.1) which is renamed to “Steering Committee”. A list of principal investigators, investigation sites, and institutions according to 1.4 of annex A is given in a stand-alone document referred to in Annex 1 of this study protocol.

Throughout this study protocol the term “study” is used as umbrella term for any systematic clinical investigation involving one or more human subjects (e.g. observational clinical investigations) whereas “trial” means any study which is interventional (e.g. by means of randomisation) and “investigation” is being used as regulatory term for any study undertaken to assess the safety or performance of a dedicated investigational product. Consequently, the term “study” will also be used in compound words in the sense described above, e.g. “study site” instead of “investigation site” or “study protocol” instead of “investigation plan”.

1.1 Steering Committee (SC)

An independent SC is responsible for scientific and medical advice of the sponsor including continuous overview of the study to assure reliability of data collected and analysed within this non-interventional, observational study. A corresponding charter defines duties and responsibilities of the SC. A list of SC members is provided in a separate document.

1.2 Clinical Event Committee (CEC)

The CEC will centrally adjudicate serious adverse events (SAEs) and adverse events (AEs) of special interest based on coded (pseudonymized) copies of corresponding medical files to assess if it fulfils criteria for defect treatment complication or being related to defect treatment. In addition, because hospitalisation decisions might be subject to local practices, social considerations, bed availability, and so on, all hospitalisations will be reviewed to assess the reason and appropriateness of each hospitalisation, i.e. whether it is “for therapy of index defect”.

A corresponding charter defines duties and responsibilities of the CEC. A list of CEC members is provided in a separate document.

1.3 Overall synopsis of the clinical study

TITLE	Suprasorb® CNP endo used for negative pressure therapy in the oesophagus and rectum to support defect and wound healing
CHIEF INVESTIGATOR	Prof. Dr. med. Mike Laukötter, Rheine
ACRONYM	Velox Study
SPONSOR	Lohmann & Rauscher GmbH & Co. KG Irlicherstr. 55, 56567 Neuwied, Germany
BACKGROUND AND RATIONALE	Anastomotic insufficiencies and oesophageal perforations are life-threatening, severe complications of the upper gastrointestinal (GI) surgery. The reported incidence of anastomotic leaks overall is between 5% and 25%. Depending on the position and dimensions of the leaks, they are associated with a mortality of up to 60% [28]. Therapy of patients who experience symptomatic intrathoracic anastomotic leaks is usually difficult and carries a high risk of severe secondary complications. Depending on the severity of the anastomotic leakage, the time interval after primary surgery, the general condition of the patient and the anastomotic location, several treatment strategies are available, such as conservative, endoscopic or surgical treatment. Conservative treatment approach includes strict nil per oral, drainage and i.v. antibiotics. Surgical treatment options span from the re-execution of the anastomosis with augmentation of the anastomotic area by vital tissue (e.g. muscle flap, omental flap), to complete surgical deviation by taking down the oesophageal conduit and creation of a cervical stoma. Endoscopic methods include injection of fibrin glue and clip administration, introduction of self-expanding metal or plastic stents and endoluminal vacuum therapy. Colorectal anastomotic leakage (CAL) also remains a frequent and dangerous complication after gastrointestinal surgery, occurring in 4-33% of patients and contributing to one third of postoperative mortality. An anastomotic defect causes leakage of colonic content into the abdominal or pelvic cavity, leading to peritonitis, abscess formation or sepsis. CAL substantially (by 1-2 weeks) prolongs hospital stay and increases medical costs by as much as US$24,000 within the first period of hospitalisation, thereby approximately tripling the expenditure in comparison to that of a normal recovery. Moreover, CAL is identified as a risk factor for local recurrence of colorectal cancer and is reported to reduce long-term cancer specific survival. The type of intervention strongly depends on the severity of CAL, which is hard to determine, and therefore the choice of intervention for a suspicious leakage is quite complex with very limited evidence-based strategy available at present. Colorectal surgeons use various methods, i.a. conservative follow-up, adhesive materials (e.g. cyanoacrylate), abscess drainage, open pelvic lavage, construction of an entirely new anastomosis, and endoscopic or surgical interventions, such as diverting or ending the stoma and transanastomotic continuous drainage system with negative pressure. Though a number of studies and case reports have demonstrated promising results regarding efficacy of EVT in treatment of both upper and lower GI tract

	perforations and anastomotic insufficiencies, and, potentially, even better safety profile of this treatment in comparison with other conventional treatment methods, the amount of data is still relatively small and additional data collection and analysis is necessary.
STUDY OBJECTIVE(S)	To assess in a routine clinical care setting the performance of Suprasorb® CNP endo regarding wound healing in patients with oesophagus and rectum defects of different aetiologies.
STUDY DESIGN	This PMCF study designed as non-interventional, observational, prospective, multicentre study in a routine clinical care setting using a marketed medical device in line with the corresponding IFU in the intended patient population.
STUDY POPULATION Medical condition/ main selection criteria	Inclusion criteria: **I1.** ≥ 18 years of age **I2.** Acute transmural defects, injuries and wounds in oesophagus or rectum, including perforations (iatrogenic or spontaneous) and anastomotic insufficiencies (Index defect) **I3.** Indication of treatment with Suprasorb® CNP endo system according to IFU and medical guidelines **I4.** Signed informed consent for usage of data Exclusion criteria: **E1.** Pre-existing coagulation disorders with increased risk of bleeding **E2.** Defects involving the bronchial system (bronchus/trachea/pulmo) **E3.** Any foreseeable deviation from IFU of Suprasorb® CNP endo **E4.** Known intolerance or allergy to one or more components of Suprasorb® CNP endo
Number of subjects	About 110 adult female and male patients with acute defects, injuries and wounds in the oesophagus or rectum and an indication of treatment with Suprasorb® CNP endo system according to IFU and medical guidelines.
Expected number of sites and countries	About 10 study sites in Germany, which are trained for the use of Suprasorb® CNP endo system treatment in routine clinical care, will screen eligible patients.
INVESTIGATIONAL INTERVENTIONS	The study protocol does not define specific study procedures for patients enrolled. Therapies and procedures during the course of this study will be performed according to the decision of the treating physician based on current applicable medical guidelines and on local policy in clinical routine care. This includes the prescription and the use of the device of interest and possible measures at enrolment and in follow-up. All devices will be used according to the corresponding IFU, only. The only study-specific obligation within this observational study is to document pre-defined medical and procedural data if available in routine clinical care in the electronic CRF (eCRF) at a level of data quality following international standards on clinical studies.

OUTCOME PARAMETERS	Primary endpoint Time period in days from index use of Suprasorb® CNP endo to release for oral food intake (in upper GI tract use) or endoscopic release for stoma relocation (in lower GI tract use). Secondary endpoints 1. Number of SAEs related to defect treatment within total observation period. 2. Number of nights in hospital for therapy of index defect. 3. Number of nights at the ICU during hospital stay for therapy of index defect.
ASSESSMENT SCHEDULEs	▪ Screening and baseline/enrolment visit (day 1). ▪ Treatment of the index defect ▪ Follow-up (FU) visits
STATISTICAL CONSIDERATIONS	In this observational study the time period from index therapy to release for oral food intake (in upper GI tract use) or endoscopic release for stoma relocation (in lower GI tract use) will be compared to published historic controls. For this, the time period is compared to published data of other EVAC and conventionally managed therapy, especially data from Wasmann et al. [29]. In addition, after half of the patients with complete follow-up, an interim analysis will be performed and sample size will be recalculated. It is expected that until then the results of a randomized clinical trial comparing an EVAC therapy to standard minimally invasive oesophagectomy (refer to NCT04162860 and [22]) will be available for adaptation of assumed confidence intervals and sample size (see 6.3.7). The hypothesis of superiority against conventionally managed therapy will be tested confirmatory. Data from all study sites will be pooled for analysis. Standard statistical methods will be used to analyse all data. Continuous variables will be summarized using the number of observations, mean, median, standard deviation, minimum and maximum values. Categorical variables will be summarized using the number of observations and percentages.
DURATION OF STUDY PERIODS	Total study duration: ▪ Enrolment period: about 24 months. ▪ Follow-up period of last patient enrolled: about 3 months. ▪ Total study period: about 27 months. Individual study duration: ▪ Expected median follow-up period: about 3 months per patient.

2. Identification and description of the investigational device(s)

This is a non-interventional, purely observational study using only marketed medical devices in line with the approved Instruction For Use (IFU) in the intended patient population. The investigational device is Suprasorb® CNP endo, used for EVAC, an endoscopic vacuum assisted therapy or endoluminal negative pressure wound therapy, assessed as class IIb (EU Quality Management System Certificate (MDR) G10 045286 0079 Rev.01) and class I medical devices (please refer to **Medicinal Product Marketing Authorisation No.**)

The Suprasorb® CNP endo therapy unit is used in combination with Suprasorb® CNP endo Kits to create, maintain, and control negative pressure and to drain body fluids in the upper and lower GI tract. EVAC can be used as intraluminal or intracavitary treatment of defects of the upper and lower GI tract. Negative pressure wound therapy drainage properties are achieved by a connection to the therapy unit with exudate canister which continuously removes secretions from wounds. The devices are available as disposable accessories for the use with the Suprasorb® CNP endo therapy unit in 4 different Kitpacks: Suprasorb® CNP endo Kit Oral, Suprasorb® CNP endo Kit Oral N, Suprasorb® CNP endo Kit Rectal and Suprasorb® CNP endo Kit AddOn. A detailed description is provided in the approved IFU.

The investigational devices will be used in routine clinical care based on the decision of the treating physician in line with IFU, medical guidelines and local policy.

3. Justification for the design of the clinical study

3.1 Medical and scientific background

Anastomotic insufficiencies and oesophageal perforations are life-threatening, severe complications of the upper gastrointestinal (GI) surgery. The reported incidence of anastomotic leaks overall is between 5% and 25%. Depending on the position and dimensions of the leaks, they are associated with a mortality of up to 60% [28]. Therapy of patients who experience symptomatic intrathoracic anastomotic leaks is usually difficult and carries a high risk of severe secondary complications. Depending on the severity of the anastomotic leakage, the time interval after primary surgery, the general condition of the patient and the anastomotic location, several treatment strategies are available, such as conservative, endoscopic or surgical treatment. Conservative treatment approach includes strict nil per oral, drainage and i.v. antibiotics. Surgical treatment options span from the re-execution of the anastomosis with augmentation of the anastomotic area by vital tissue (e.g. muscle flap, omental flap), to complete surgical deviation by taking down the oesophageal conduit and creation of a cervical stoma. Endoscopic methods include injection of fibrin glue and clip administration, introduction of self-expanding metal or plastic stents and endoluminal vacuum therapy.

As one can see already from the number of possible options, no general treatment of choice or standardized treatment algorithm exists so far. Each method has its pros and contras. While some surgeons recommend aggressive surgery, others prefer conservative approaches, including peri-anastomotic drainage, total parenteral nutrition, nasogastric decompression, and use of broad-spectrum antibiotics. Also, although introduction of self-expanding metallic coated stents was regarded as a considerable advancement in treatment of thoracic anastomotic leaks, their usage does not always lead to a sufficient sealing of the leakage, and dislocation rates up to 30% have been reported [27]. Another limiting factor for the stent placement may be a need for additional surgical interventions to provide drainage and removal of the septic focus [25, 27, 31].

Colorectal anastomotic leakage (CAL) also remains a frequent and dangerous complication after gastrointestinal surgery, occurring in 4-33% of patients and contributing to one third of postoperative mortality. An anastomotic defect causes leakage of colonic content into the abdominal or pelvic cavity, leading to peritonitis, abscess formation or sepsis. CAL substantially (by 1-2 weeks) prolongs hospital stay and increases medical costs by as much as US$24,000 within the first period of hospitalisation, thereby approximately tripling the expenditure in comparison to that of a normal recovery. Moreover, CAL is identified as a risk factor for local recurrence of colorectal cancer and is reported to reduce long-term cancer specific survival.

The type of intervention strongly depends on the severity of CAL, which is hard to determine, and therefore the choice of intervention for a suspicious leakage is quite complex with very limited evidence-based strategy available at present. Colorectal surgeons use various methods, i.a. conservative follow-up, adhesive materials (e.g. cyanoacrylate), abscess drainage, open pelvic lavage, construction of an entirely new anastomosis, and endoscopic or surgical interventions, such as diverting or ending the stoma and transanastomotic continuous drainage system with negative pressure.

3.2 Rationale

Endoscopic (endoluminal) vacuum therapy (EVT), alternative term endoscopic vacuum-assisted closure (EVAC), was for the first time applied in Europe by Weidenhagen et al. [31] in 2003 for use in the rectum and in 2007 by Loske et al. [12] for use in the foregut.

Loske et al. [13] summarized the experience of EVT for patients with anastomotic insufficiency secondary to esophagectomy or gastrectomy (n=5), iatrogenic oesophageal perforation (n=2), oesophageal wall necrosis (n = 1), Boerhaave's syndrome (n=1), and perforation of oesophageal cancer (n=1). After one to seven changes of the sponge at intervals of 2–7 days and a mean therapy duration of 12 days, the defects were healed in all the surviving patients (n=9). One patient died of intercurrent severe colitis. In three cases, a revision laparotomy was necessary at the beginning of treatment. No post-interventional stricture or functional relevant scar formation was observed during a follow-up period of 10 – 380 days after termination of the vacuum therapy.

In a pilot study of EVT in the upper GI tract, conducted by Ahrens et al. [1], four patients with thoracoabdominal oesophagus resection and one patient with myotomy of Zenker's diverticulum were successfully treated till closure of their leakages without a need for surgical re-intervention. Two patients required endoscopic dilation of moderate anastomotic stenosis after completion of EVT.

Wedemeyer et al. [30] could demonstrate successful use of EVT in the management of major postsurgical gastrooesophageal intrathoracic leaks (prospective single-centre study with 8 patients). Leakage closure by EVT was achieved in 7 cases, EVT could not be completed in one case due to safety concerns. No SAEs associated with the endoscopic intervention or EVT were noted. Complications observed: patients reported discomfort in the nose and throat (n=8), sponge dislocation (n=2).

In the retrospective analysis by Brangewitz et al. [6], comparing EVT versus stent management (self-expanding metal (SEMS) or plastic stents (SEPS)), data of 39 patients who were treated with SEMS or SEPS and 32 patients who were treated with EVT for intrathoracic leakage were analysed. Successful wound closure was independently associated with EVT (hazard ratio 2.997, 95% confidence interval [95%CI] 1.568–5.729; P=0.001). The overall closure rate was significantly higher in the EVT group (84.4%) compared with the SEMS/SEPS group (53.8%). No difference was found for hospitalisation and hospital mortality. Significantly more strictures were observed in the stent group (28.2% vs. 9.4% with EVT, P<0.05). Complications in the stent group constituted: stent dislocation (n=6), anastomotic stricture (n=11), severe bleed at the upper end of the stent followed by immediate surgical revision (n=1), oesophageal necrosis with fatal outcome (n=1), self-limiting bleeding after stent-removal (n=2), ulcers after stent removal, not requiring specific therapy (n=5). Complications in the EVT group constituted: sponge dislocation (n=5), bleeding after sponge removal (n=1), significant mucosal tear proximal to the anastomosis during sponge removal (n=1), bronchooesophageal fistula with later required surgery (n=1), anastomotic stricture (n=3).

Heits et al. [8] analysed data of 10 patients, treated by EVT for oesophageal perforations, located in the cervical (n=3) and thoracic (n=7) oesophagus. Complete healing of the wound was achieved in 9 cases. One patient has died (failure of the cardiovascular system caused by a known heart insufficiency). EVT-associated complications (mediastinal emphysema) occurred in 7 patients.

Bludau et al. [4] summarized the experience of EVT for patients with oesophageal leakages (n=14). For 6 of 14 patients, EVT was combined with a placement of self-expanding metal stents. Complete closure of the

oesophageal defect was achieved in 12 cases. Two patients died due to prolonged sepsis before EVT could be completed. In two cases, oesophageal stenosis was diagnosed, which was treated successfully by one-time pneumatic dilation. No other complications related to the EVT were observed.

Strangio et al. [26] evaluated performance and safety of EVT in 25 patients with partial colonic anastomotic leakage. Complete healing was achieved in 22 cases. Three patients developed a major complication (1 ureteric fistula, 1 ileal fistula, and 1 pararectal abscess), all successfully treated by surgery. Ileostomy closure was achieved in 11 patients. No mortality related to the procedure was observed.

In a retrospective study including 15 patients with pelvic anastomotic leakage after colorectal surgery [9], lumen integrity was achieved in 12 cases. Treatment was discontinued due to progression of pelvic sepsis in two patients and due to bleeding in one patient. No complications, related to the EVT, were reported.

In a study of EVT by upper gastrointestinal leaks and perforations, conducted by Smallwood et al. [25], complete closure of perforation or leak after an average of 35.8 days of EVT was demonstrated for all patients (n=6). No deaths occurred within 30 days following EVT. One patient died following complete closure of his perforation and transfer to an acute care facility due to an unrelated complication. There were no complications directly related to the use of EVT.

Mennigen et al. [20] compared 30 patients, treated with stent insertion, with 15 patients, treated with EVT for management of oesophageal anastomotic leakage following oesophagectomy, performed with a stapled intrathoracic anastomosis (end-to-side, circular stapler). The rate of endoscopic anastomotic healing was found to be higher for endoscopic vacuum therapy (93.3%, vs. 63.3% in a stent group; P=0.038). No significant difference was observed for overall mortality, duration of therapy, and length of hospitalisation.

In a prospective cohort study [11] including 52 patients with oesophageal anastomotic insufficiencies of different origin, healing of the oesophageal wall defects in 49 cases was observed (in 7 cases, final closure was performed by additional clipping of residual superficial defects with an Over-The-Scope-Clip [OTSC]). One patient showed no response to EVT and two patients died due to haemorrhage related to the procedure. Post-interventional stricture was observed during follow up period in 4 patients.

In a retrospective review of case series [3], endoscopic vacuum therapy was applied in 14 patients with colorectal leak. Overall success rate was 79%, favored by early beginning of treatment. Median duration of treatment was 12.5 sessions (range 4 – 40). Median time for complete healing was 40.5 days (range 8 – 114). No EVT-related complications were observed.

The effectiveness and safety of EVAC therapy was verified in a study including 55 patients with anastomotic leakage in the upper GI tract [32]. Patients underwent elective oesophageal resection and EVAC (intracavitary or intraluminally) was initiated. Sponge changes were performed either every 3 days for intracavitary localization or every 5 – 7 days for intraluminal position. Successful closure was achieved in 49 patients (n=49) while complication rate was 5.4 % (n=3). One patient suffered from bleeding while 2 patients had minor sedation-related complications. Median number of EVAC procedures was 3 with median 14-day duration of therapy. Mortality rate was 7.2 % (n=4); 3 patients died despite of complete healing due to multiple organ failure, acute respiratory distress syndrome and urosepsis.

In the prospective, observational, national, multicenter registry of Eso-Sponge® for anastomotic leakage after esophageal resection or perforation (23) a success rate of 91 % was demonstrated.

In 2019, Loske (18) summarized the data from 18 studies (420 patients worldwide) in which more than five patients were treated with endoscopic negative pressure therapy in the upper gastrointestinal tract, and the success rate was found to be 87% (range 60-100%).

A systematic search of MEDLINE/PubMed and Cochrane databases (10) was performed by Kühn et al. using search terms related to EVT and colorectal defects (anastomotic leakage, rectal stump insufficiency) according to the PRISMA guidelines. Randomized controlled trials (RCTs), observational studies, and case series published by December 2020 were eligible for inclusion. A meta-analysis was conducted on the success of EVT, stoma reversal rate after EVT as well as procedure-related complications. Twenty-four studies reporting on

690 patients with colorectal defects undergoing EVT were included. The mean rate of success was 81.4% (95% CI: 74.0%-87.1%). The proportion of diverted patients was 76.4% (95% CI: 64.9%-85.0%). The mean rate of ostomy reversal across the studies was 66.7% (95% CI: 58.0%-74.4%). Sixty-four patients were reported with EVT-associated complications, the weighted mean complication rate across the studies was 12.1% (95% CI: 9.7%-15.2%).

Also, numerous case reports and case series describe the successful usage of EVT for closure of oesophageal [7, 14, 15, 16, 17, 21, 30] and rectal [2, 5] defects.

Only limited evidence for comparison of different treatment approaches for both upper and lower GI tract defects can be found in literature. To compare EVT of leakage after oesophagectomy with other therapy regimes, Schniewind et al. [24] analysed 62 patients, who have developed an anastomotic leak. Therapy options included surgical revision (n=18), endoluminal vacuum therapy (n = 17), endoscopic stent application (n=12), and conservative management (n=15). In-hospital mortality constituted 26% (of which EVT 12% [n=2], surgery 50% [n=9], stent 42% [n=5], 0% of the conservatively treated patients). The survival in the EVT group was significantly superior to that of the surgically treated patients (p = 0.011, log rank test) and to that of the stented patients with oesophageal leakage (p =0.00014, log rank test). To summarize, this study suggests that EVT is an effective procedure for a management of major leakage from oesophageal anastomoses and might be superior to surgical revision and stent placement, especially in septic patients. However, it is obvious that this data should be further confirmed on bigger patient population.

In the study by Mees et al. [19] comparing patients treated with EVT (n=5: rectal carcinoma n=3, ulcerative colitis n=2) vs. transrectal lavage (n=5: rectal carcinoma n=3, ulcerative colitis n=2) after colorectal resection, median time of defect closure constituted 45 days in the EVT group, compared to 101 days in the lavage group. Average time in the hospital constituted 37 and 45 days, respectively. EVT was well tolerated by all patients and no specific side effects during or after the therapy were observed. One patient in the EVT group developed a mild rectal stenosis in the anastomotic area during the follow-up. This stenosis was treated by self-dilatation using Hegar's dilator for 4 weeks. Overall costs were summarized for both procedures considering the differences in the number of sessions (EVT - 7 replacements/ patient; lavage - 12 procedures/ patient), costs for staff and material. This resulted in comparable costs of 122.85 € (EVT) vs. 119.4 € (lavage), respectively.

Though a number of studies and case reports have demonstrated promising results regarding efficacy of EVT in treatment of both upper and lower GI tract perforations and anastomotic insufficiencies, and, potentially, even better safety profile of this treatment in comparison with other conventional treatment methods, the amount of data is still relatively small and additional data collection and analysis is necessary.

4. Benefits and risks of investigational device, clinical procedures and clinical study

All medical devices used in this study are CE-marked, marketed devices which will only be used in line with the approved IFU in the intended patient population.

4.1 Anticipated clinical benefits of investigational devices

Patients requiring EVAC are considered to be in a life-threatening condition due to the possibility of developing mediastinitis, peritonitis as well as consecutive sepsis with fatal outcome. With regard to the benefits of Suprasorb® CNP endo, review of current literature allows the conclusion that safety and tolerability of the IP are acceptable. Therefore, the IP can be considered suitable for the management of endoluminal wounds including perforations and anastomotic leakages. There is sufficient clinical evidence to declare conformity of the device with the general safety and performance requirements.

4.2 Anticipated adverse effects of investigational devices

4.2.1 Side effects

The biocompatibility of Suprasorb® CNP endo can be classified as acceptable for the intended purpose and application. Suprasorb® CNP endo is made of materials which have been well-characterised chemically and physically in the published literature. Overall, the combination of non-clinical and clinical data on Suprasorb® CNP endo demonstrates that Suprasorb® CNP endo devices are suitable for their intended purpose and confirms that the clinical benefits of the device outweigh theoretical and known risks.

The most common complications recorded for the devices are, e.g. pain, nasal bleeding and mediastinal emphysema. However, the devices showed to be feasible and well-tolerated device for EVAC. It should be kept in mind that patients requiring EVAC are considered to be in a life-threatening condition due to the possibility of developing mediastinitis, peritonitis as well as consecutive sepsis with fatal outcome.

4.2.2 Interactions

None known.

4.3 Effects of study participation

4.3.1 Anticipated risks of study participation

Participation does not pose additional risks compared to routine clinical care because there are no study interventions in this purely observational clinical study. Participation just means following routine clinical care decisions and procedures but allowing to use available medical data in a central study database.

- All medical devices used in this study are marketed products used in clinical routine care in line with market authorisation and represent standard of care in this therapeutic indication. This also applies to all medical procedures within the study.
- This clinical study is purely observational. The study protocol does not define any study-specific intervention or procedure to be performed. The only study-specific obligation within this observational study is to document pre-defined medical and procedural data if available in routine clinical care at a level of data quality following international standards on clinical studies.
- All therapeutic decisions and procedures are performed as routine clinical care following all applicable ethical and regulatory standards. Therefore, adverse events will occur in clinical manifestations and at rates as in routine clinical care.
- The study will be conducted in accordance with the principles laid down in the Declaration of Helsinki in its version of October 2013 (Fortaleza) and in accordance with ISO 14155:2020.
- Before initiating the study in a country, approval of the corresponding Ethics Committees (ECs) will be obtained.

4.3.2 Anticipated benefits of study participation

No to minor additional benefit will be added for patients participating in this purely observational clinical study.

- All therapeutic decisions and procedures are following individual decisions of the treating physician and are performed as routine clinical care. Thus, no additional benefit compared to routine clinical care will occur because all procedures are routine clinical care.

- Little additional benefit might occur based on standardised data documentation and queries related to data entries provided by a third party (e. g. a contract research organisation) which both might lead to more standardised routine clinical care procedures and decisions.

4.4 Possible interactions with concomitant medical treatments

None known.

4.5 Steps that will be taken to control or mitigate the risks

All therapeutic decisions and procedures are following individual decisions of the treating physician and are performed as routine clinical care practice following applicable medical standards. All relevant safety information concerning residual risks is provided to the user in the product labelling and instructions for use. This comprises contraindications, side effects, warnings and precautions.

The study protocol does not define any study-specific intervention or procedure to be performed. Therefore, adverse events representing the potential risks are expected to occur in clinical manifestations and at rates as in routine clinical care. The investigator will promptly report to the sponsor serious adverse events and adverse device effects according to 14.3. The sponsor will, based on these data, perform actions in case of hazards and foreseeable damage to patients and report promptly to regulatory bodies according to 14.3.

4.6 Rationale for benefit-risk ratio

The study is purely observational with documentation of routine clinical care procedures and outcomes, without adding any study specific interventions or procedures. Thus, the structural risk of the study defines as low, i.e. not exceeding the risk of use of Suprasorb® CNP endo in routine clinical care.

From Clinical Evaluation Report (DI_CER_00020_02, Feb 2022) and risk management perspective it can be concluded that the benefit / risk ratio for Suprasorb® CNP endo is positive.

5. Objectives and hypotheses of the clinical study

5.1 Purpose of the clinical study, claims for clinical performance, effectiveness or safety of the investigational device

5.1.1 Purpose

The study is performed as observational PMCF study to generate in the setting of routine clinical care reliable data on the therapeutic approach of Suprasorb® CNP endo used in adult patients for negative pressure therapy in the oesophagus and rectum to support defect and wound healing. It will comply with the requirements set out by the clinical data requirements of EU MDR 2017/745.

5.1.2 Claims for clinical performance and effectiveness

The Suprasorb® CNP endo claims to support defect and wound healing in the upper and lower gastrointestinal tract by draining body fluids and simultaneously provide the possibility of enteral feeding for the upper gastrointestinal tract. Defects like perforations (iatrogenic perforations, spontaneous perforations), anastomoses and anastomotic insufficiencies can be treated intraluminal and/or intracavity with Suprasorb® CNP endo.

5.1.3 Claims for clinical safety

There is sufficient clinical data to declare conformity of the IP with the general safety and performance requirements with a positive benefit / risk ratio.

5.2 Objectives

The objectives of this PMCF study are to confirm performance and safety of Suprasorb® CNP endo in routine clinical care by evaluation of clinical data after market approval, including detection of potential unexpected adverse events associated with its use within the certified indications and under the conditions of routine clinical care. This will be assessed in defects of different aetiology in the oesophagus and rectum, thus, widely representing routine clinical care population and use.

5.2.1 Primary objective

To assess in a routine clinical care setting the performance of Suprasorb® CNP endo regarding wound healing in patients with oesophagus and rectum defects of different aetiologies.

Wound healing is defined as release for oral food intake (in upper GI tract use) or endoscopic release for stoma relocation (in lower GI tract use).

Time to wound healing is consequently defined as time from index use of Suprasorb® CNP endo to date of release for oral food intake (in upper GI tract use) or endoscopic release for stoma relocation (in lower GI tract use).

5.2.2 Secondary objectives

To assess in a routine clinical care setting in this patient population

1. adequate safety of the use of Suprasorb® CNP endo, and
2. duration of hospital care with use of Suprasorb® CNP endo.

5.2.3 Hypotheses to be accepted or rejected by statistical data from the study

The primary hypothesis is that the time period from index therapy to release for oral food intake (in upper GI tract use) or endoscopic release for stoma relocation (in lower GI tract use) will be superior to historic controls from literature reporting standard management of therapy without use of EVAC therapies.

A Statistical Analysis Plan (SAP) will be prepared prior to start of data analysis detailing the statistical analysis methods which will be used.

5.3 Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits

This observational study will provide information on “real world” use and practice in treatment of both upper and lower GI tract perforations and anastomotic insufficiencies using the Suprasorb® CNP endo system in a routine clinical care setting.

The indication for this treatment is decided in acute clinical situations needing urgent treatment, thus, a controlled clinical trial setting will be impractical and may lead to a larger selection bias compared to a study which reports observation of routine clinical care without pre-defined study procedures and interventions.

The study will only be performed in study sites which are trained for the use of the Suprasorb® CNP endo system treatment in routine clinical care and generally experienced in use of EVT for treatment of upper or

lower GI tract perforations and anastomotic insufficiencies. Thus, comparability in selection of patients, decision on indication and procedures performed can be presumed.

5.4 Risks and anticipated adverse device effects that are to be assessed

The investigational device is a marketed, CE-certified product, which will be used within its intendent purpose. Rate of defect treatment complications (during index defect treatment and in follow-up treatments) and rate of SAEs related to defect treatment will be assessed. The term “defect treatment related” represents not only device-related but in total procedure-related AEs of special interest and SAEs. Non-serious AEs which are not classified as “of special interest” will not be assessed.

6. Design of the clinical study

6.1 General

6.1.1 Study design

This PMCF study designed as non-interventional, observational, prospective, multicentre study in a routine clinical care setting using a marketed medical device in line with the corresponding IFU in the intended patient population.

The routine clinical care of study patients is in no way influenced by their participation in this study. All clinical procedures and therapies are based on individual decisions of the treating physician following current applicable medical guidelines and local policy, not pre-defined in the study protocol. Thus, this clinical study is purely observational.

Patients will be screened at study sites, which have expertise in treatment of oesophageal and / or intestinal defects and are trained for the use of Suprasorb® CNP endo treatment.

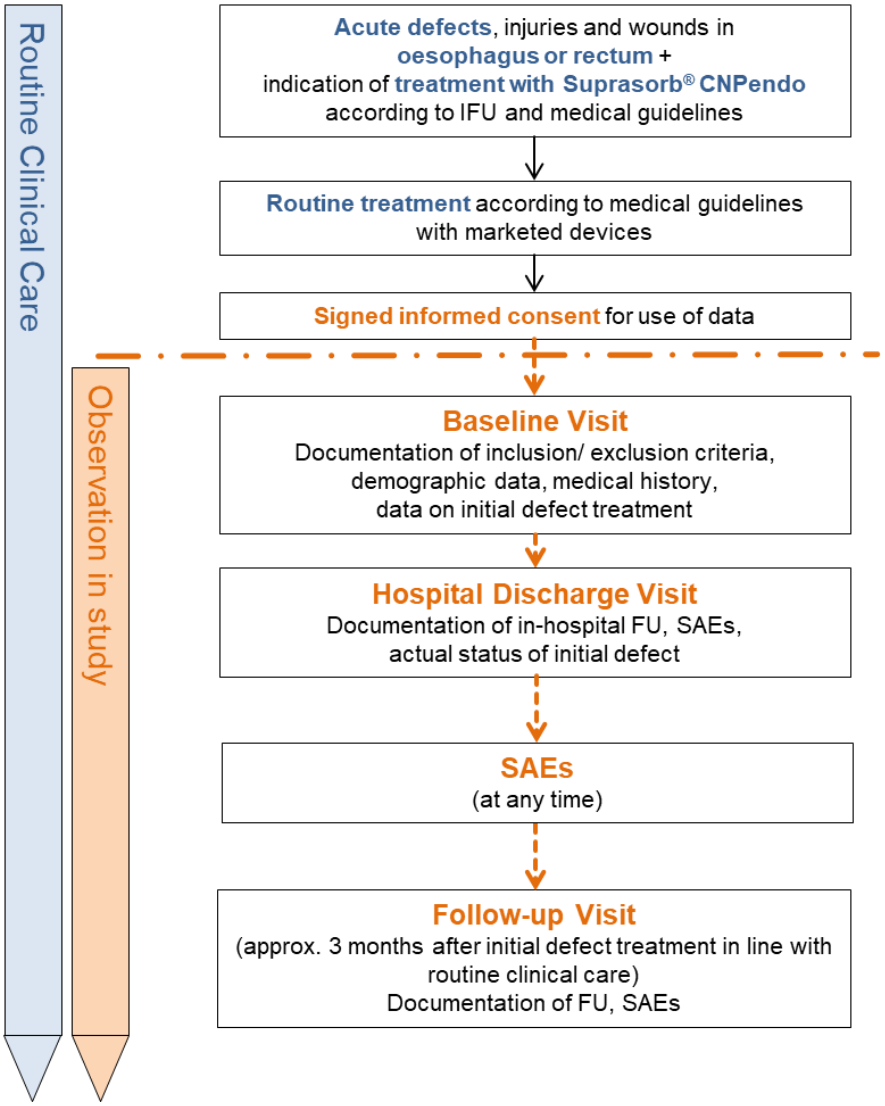
Patients will be enrolled in this non-interventional study if an indication for Suprasorb® CNP endo treatment was defined by the treating physician based on routine clinical care decisions, all inclusion and no exclusion criteria are met and written consent is given to use and process their routine clinical data according to data privacy standards.

In most cases, enrolment into the study will take place after Suprasorb® CNP endo treatment related to the fact that the treatment decision for such patients is often made in a medically acute situation. A screening form will be used by the study site staff to document some anonymised data of all potentially eligible patients together with a reason if not participating in the study to control selection bias and to maintain prospective data generation.

Patients will be diagnosed and evaluated for eligibility in routine clinical care by expert centres in the indication of interest and enrolled competitively by all authorised study sites without pre-defined quota for individual study sites.

The study protocol does not define specific study procedures for patients enrolled. Therapies and procedures during the course of this study will be performed according to the decision of the treating physician based on current applicable medical guidelines and on local policy in clinical routine care. This includes the prescription and the use of the device of interest and possible measures at enrolment and in follow-up. All devices will be used according to the corresponding IFU, only. The only study-specific obligation within this observational study is to document pre-defined medical and procedural data if available in routine clinical care in the electronic CRF (eCRF) at a level of data quality following international standards on clinical studies.

Flowchart



6.1.2 Measures to minimize or avoid bias

The study site will document all consecutive patients, for whom treatment of acute oesophageal or intestinal defects using Suprasorb® CNP endo treatment is clinically indicated. If a potentially eligible patient refuses to consent participation in the study or other reasons for non-participation are existing, the patients' minimum of medical data (age, sex, indication for treatment of interest) will be documented in a Screening Log located at the study site for potential review e.g. by clinical monitors of the CRO to check for potential selection bias. The data in the Screening Log will not be processed centrally.

6.1.3 Endpoints of the study

6.1.3.1 Primary endpoint

Time period in days from index use of Suprasorb® CNP endo to release for oral food intake (in upper GI tract use) or endoscopic release for stoma relocation (in lower GI tract use).

In case of lower GI tract use and no stoma present, time period to release for oral food intake is the relevant endpoint.

6.1.3.2 Secondary endpoints

1. Number of SAEs related to defect treatment within total observation period.
2. Number of nights in hospital for therapy of index defect.
3. Number of nights at the ICU during hospital stay for therapy of index defect.

Nights at an intermediate care unit (IMC) will not count for this secondary endpoint.

SAEs will be adjudicated by an independent Clinical Event Committee (CEC) according to standard definitions. Wherever reasonable, endpoints will be normalised to one year of follow-up to adapt results to varying follow-up periods.

"**Index defect**" describes for each study patient the defect(s) which lead to the clinical indication of treatment with Suprasorb® CNP endo system according to IFU and medical guidelines as defined in 6.3.1.

"**Index therapy**" describes for each study patient the first use of Suprasorb® CNP endo for therapy of the index defect.

6.1.4 Methods and timing for assessing, recording, and analysing variables

Only data which can be obtained from routine clinical care files of the patients will be recorded. Data of routine clinical care visit after study enrolment will be reported in the e-CRF. Data will be derived from clinical records and findings, radiological assessments, observations or other sources (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes).

Within this observational study timing of measures and clinical data to be reported are determined by routine clinical care in line with applicable medical guidelines and local policies. The study protocol just defines some procedural recommendations.

6.1.5 Equipment to be used for assessing the study variables

Only data which are obtained in routine clinical care will be recorded and reported in the eCRF. Thus, no special equipment differing from routine clinical care will be used to assess the study variables.

6.1.6 Any procedures for the replacement of subjects

No study-specific intervention is defined within this observational study which is only following routine clinical care.

Patients' written informed consent to use and process their routine clinical care data according to data privacy standards will be obtained prior to documentation of any patients' data in the e-CRF. It is expected that in the majority of patients written informed consent to use and process data (enrolment) is provided after index therapy.

The principle for analysis of study data is intention to treat without restrictions to any subsequent course of follow-up.

Thus, no necessity of any procedures for the replacement of patients is foreseeable.

6.2 Investigational device(s) and comparator(s)

In this purely observational study no investigational devices will be used. However, a marketed medical device of interest will be used upon the investigator's decision according to medical guidelines and local policies. All medical devices used in this study are CE-marked, marketed devices which will only be used within the approved IFU in the intended patient population.

In this purely observational study without pre-defined therapy groups, no control group is defined, thus, no comparator devices are used.

Other medical devices which might be used reflect the medical decision of the investigator but are not defined or specified within the study protocol.

6.3 Subjects

About 110 adult female and male patients with acute defects, injuries and wounds in the oesophagus or rectum and an indication of treatment with Suprasorb® CNP endo system according to IFU and medical guidelines will be enrolled. Patients' written informed consent to use their routine clinical data according to data privacy standards must be obtained prior to documentation of patients' data in the e-CRF. All patients in whom the device has been used will be followed during routine clinical practice and will visit a site only in the course of their routine clinical care. No additional treatment or medical examinations will be performed.

It will be assured by means of the e-CRF system that treatments of upper GI tract and lower GI tract will be about equally balanced over the total study population.

6.3.1 Inclusion criteria

I1. ≥ 18 years of age

I2. Acute transmural defects, injuries and wounds in oesophagus or rectum, including perforations (iatrogenic or spontaneous) and anastomotic insufficiencies (Index defect)

I3. Indication of treatment with Suprasorb® CNP endo system according to IFU and medical guidelines

I4. Signed informed consent for usage of data

6.3.2 Exclusion criteria

E1. Pre-existing coagulation disorders with increased risk of bleeding

E2. Defects involving the bronchial system (bronchus/trachea/pulmo)

E3. Any foreseeable deviation from IFU of Suprasorb® CNP endo

E4. Known intolerance or allergy to one or more components of Suprasorb® CNP endo

6.3.3 Criteria and procedures for subject withdrawal or discontinuation

Patients enrolled into the study can withdraw consent for use of their data at any time for any reason without prejudice to further treatment or level of care. The investigator is not able to decide about the discontinuation of study participation of any patient. In the event that a patient withdraws consent, the date and reason for termination will be documented in the e-CRF according to ISO 14155:2020, section 7.10. In case of withdrawal of consent for use of data, no further data will be collected from the patient. The withdrawal of the informed consent shall not affect the use of data based on informed consent before its withdrawal. All reasonable efforts should be made to complete assessments and retrieve any outstanding data.

Due to observational nature of the study no specific procedures for follow-up of subjects following the end or a temporary or early termination of the study are defined. All medical care after withdrawal, discontinuation or regular end of the observation will be provided by the treating physician according to routine clinical care.

6.3.4 Point of enrolment (study sites)

About 10 study sites in Germany, which are trained for the use of Suprasorb® CNP endo system treatment in routine clinical care, will screen eligible patients.

Patients will be enrolled in this observational study if an indication for Suprasorb® CNP endo treatment was defined by the treating physician based on routine clinical care decisions, all inclusion and no exclusion criteria of the study are met and written consent is given to use and process their routine clinical data according to applicable data privacy standards.

It is expected that in the majority of patients written informed consent to use and process data is provided after routine clinical treatment of the index defect.

6.3.5 Total expected duration of the study.

The clinical phase of the study (first patient in to last patient out) is expected to last for 27 months with 24 months of enrolment and 3 months of follow-up of last patient in. After about 3 months of follow-up of the last patient treated with index therapy and subsequent final data cleaning, global end of study will be declared.

6.3.6 Expected duration of each subject's participation

The mean follow-up period (from date of enrolment to end of follow-up) of all patients is expected to be about 3 months.

6.3.7 Number of subjects required to be included in the study

As discussed in 3.2, the evidence for the different treatment options is very limited. Especially the patient populations, e.g. regarding underlying diseases, as well as the processes in the therapy are very different in the individual studies published. Therefore a reasonable sample size calculation is not possible at the moment. Thus, an interim analysis with sample size re-calculation is planned.

The best evidence for an **initial sample size calculation** is provided by data of the study by Wasmann et al. [29], a cohort study including 334 patients with ileal defects, where EVAC therapy was compared to conventional management of defect treatment. The median time to stoma relocation was estimated as 4 months in the EVAC group (interquartile range 3 to 6 months) versus 4 months (3 to 13 months) in the conventional management group. Therefore, the proportion of patients with stoma relocation after 6 months is known as 75% in the EVAC group. Assuming a constant increasing proportion in the conventional management group from 4 to 13 months with 2.8% per month, a proportion of 56% stoma relocations after 6 months is expected for the conventional group. Even if the follow-up is set to 3 months in this study, sample size calculation can be based on 6 months results.

Sample size calculation was performed with PASS 16.0.3 using a two-sided, one-sample log rank test. A group sequential design with the alpha spending function of O'Brien-Fleming results in a two-sided type one error of 4.92% for the final analysis. A sample size of 99 analysable subjects achieves 80% power to detect shorter time to release for food intake or endoscopic release for stoma relocation (assuming a proportion of relocated stoma of 75% after 6 months in the EVAC group when the proportion in the historic control group is 56%). The expected number of events during the study with 3 months of follow-up is 13. It is assumed that the survival time distributions of both groups are approximated reasonable well by the Weibull distribution with a shape parameter of 1.00. To account for treatment switching and early drop-outs of 10%, 110 analysable patients will be enrolled.

After data of complete follow-up of about half of the enrolled patients are available, an interim analysis will be performed and sample size will be recalculated. It is expected that until then the results of an ongoing randomized clinical trial comparing EVAC therapy to standard minimally invasive esophagectomy (refer to NCT04162860 and [22]) are available and can also be used as more reliable assumptions for sample size recalculation. The maximum sample size is set to 1.5 times the initial sample size, equal to 165 patients.

6.3.8 Estimated time needed to select this number (i.e. enrolment period)

It is expected that about 24 months of enrolment will lead to about 110 patients enrolled.

6.4 Procedures

6.4.1 Study-related procedures

No study-specific procedures are defined in this protocol and will be performed during this observational study but routine clinical care procedures according to applicable medical guidelines, IFU of the devices used and local policy.

"**Enrolment**" in this observational study means the patient is giving informed consent for use of personal medical data, i.e. the legal prerequisite for being part of this clinical observation. Thus, "**date of enrolment**" is the date of the signature on informed consent. In this purely observational study consent for use of data might be given after index treatment because this treatment is performed in routine clinical care without any study-specific requirements or definitions and might be performed in an acute setting.

"**Baseline visit**" in this observational study is not a specific personal visit of the patient at the study site but a basket to document all relevant data known at baseline. Thus, medical data reported at baseline visit might represent patient's status even before enrolment, e.g. data on medical history. Use of these data is covered by the informed consent given by the patient.

Due to the acute defects in focus and the corresponding indication of invasive treatment in this purely observational study, "date of enrolment" (=date of informed consent for use of personal medical data) might therefore be after "**date of index treatment**".

"**Start of observation**" with respect to the objectives and endpoints of this study is the time point of the index treatment.

6.4.2 Pre-Screening/check of eligibility

Routine clinical care patients are pre-selected and diagnosed for potential eligibility of study participation based on existing data generated in routine clinical care which is not part of this observational study. However, all potentially eligible patients irrespective of their subsequent enrolment into this study will be documented in a screening log within the time period while the study site is open for recruitment to control for selection bias (refer to 6.1.2).

6.4.3 Screening and baseline/enrolment visit (day 1 of observation)

Patients will be screened and enrolled by contracted study sites only, i.e. expert centres. Screening of potentially eligible patients will be performed within routine clinical care. Check for eligibility according to in- and exclusion criteria will be performed using routine clinical care data.

Potentially eligible patients will be informed about the use of their medical data in the study. The patient will be given sufficient time to consider the implications of data use before deciding whether to consent. Participation in this study means following clinical routine care procedures, but allowing for documentation of medical data in a central web-based data base (e-CRF). If the patient is willing to agree, the informed consent form for data use will be provided for signature. As soon as signed informed consent is available, the patient has been enrolled into the study.

Informed consent for use of personal medical data will often be given after the date of index treatment because the treatment is performed in routine clinical care. The fact of enrolment and the enrolment date will in any way be documented within the baseline visit.

After signing the consent, patients are checked for eligibility according to in- and exclusion criteria by the participating sites consecutively to minimise selection bias. Study relevant data will be reported in the e-CRF. The e-CRF system will automatically display the patient ID as consecutive number across all participating study sites, i.e. without reference to the recruiting site.

The following data items will be documented of each participating patient at enrolment:

- Demographic data
- Patient's physical status
- Medical history
- Relevant concomitant medication and diseases

Data on the entire clinical stay for treatment of the index defect will be documented.

6.4.4 Treatment of the index defect

The decision of treatment of the index defect lies with the treating physician in routine clinical care. Indication as well as initiation of treatment should follow applicable medical guidelines, local clinical care policy and the IFUs of the devices used.

Initiation of treatment might start as routine clinical care procedure before enrolment into the study (i.e. informed consent of the patient) but data can be entered into the e-CRF after signed informed consent is available (i.e. after enrolment), only.

- **Primary EV therapy** is defined as the utilisation of EVT as first-line therapy for perforation or leak.
- **Rescue EV therap**y is defined as EVT placement following failure of definitive surgical repair for a perforation or leak.
- **Defect closure following EVT placement** is defined as 1) no evidence of continued leak under direct endoscopic visualization and 2) a negative oesophagram following discontinuation of EVT therapy.

Data regarding index defect, related therapy and outcome following EVT placement will be documented in the e-CRF at the Index-treatment visit.

The following data items will be documented of each participating patient at the index-treatment visit:

- Data of index treatment and related therapy (defect size, type and location of perforation, pre-existing pathology, ASA-classification, Perforation Severity Score (PSS), primary or rescue EVT application, type of endo-sponge placement, type of surgical repair, time to placement of EVT following diagnosis, number of EVT changes, number of days between EVT changes, total length of EVT therapy, relevant laboratory parameters)
- Outcome of index treatment (including 30-day mortality, closure interventions following treatment of index defect, hospital length of stay (LOS), ICU LOS, EVT therapy-specific findings (e.g. migration, dislodgement, erosion), time to oral diet initiation / endoscopic release for stoma relocation following successful defect closure).

6.4.5 Follow-up (FU) visits

Every patient will be followed for 3 months after discharge after index treatment.

In line with routine clinical care, at least one personal follow up visit should take place within 3 months of follow up. To ensure comparability of data, in case this follow up visit has not been performed after 3 months (± 2 weeks) in addition a phone call with the patient should provide final information to be documented in the FU visit (phone) of the e-CRF.

At the FU visits the following data from clinical routine will be documented in the e-CRF (if available):

- Patient status
- Relevant concomitant medication and other treatment
- Safety related events: SAEs (including SADEs), AEs of special interest (including ADEs) and DD

6.4.6 Visit table

Assessments*	**Baseline visit**	**Index-Treatment**	**FU visits**
Informed consent for data use	X		
In- and Exclusion criteria	X		
Demographic data	X		
Medical history	X		
Patient's status	X		X**
Medication/other treatment	X	X	X**
Concomitant diseases	X		
Data regarding index treatment and related therapy		X	
Outcome of index treatment		X	
Safety related events (SAEs, SADEs, ADEs, DD)		X	X

* If data are available in routine clinical care.

** Only if the FU-Visit is performed on site

6.4.7 Activities performed by sponsor representatives (excluding monitoring)

The sponsor will define potentially eligible hospitals and physicians for participation in this study based on his knowledge on their training and expertise in use of the Endoscopic (Endoluminal) Vacuum Therapy in the gastrointestinal tract treatment in routine clinical care. Eligibility of each study site according to standards following ISO 14155:2020 will be assessed and documented by the responsible CRO.

No other activities of sponsor representatives related to this study will be performed.

6.4.8 Known or foreseeable factors that may compromise the outcome of the study or the interpretation of results

This clinical study is purely observational. All procedures and therapies are representing routine clinical care based on individual decisions by the treating physician and are not given as standardised procedures in the study protocol. It is expected that observed variations in diagnosis and treatment of defects of interest will be further compared to controlled clinical trials with given standards. Selection bias will be controlled by means of data collected about the site itself and pooled details about their patients of interest in routine clinical care.

The data of this study represent routine clinical care of patients with acute defects, injuries and wounds in the oesophagus or rectum, including perforations (iatrogenic or spontaneous) and anastomotic insufficiencies without limitations normally given by protocol definitions of controlled clinical trials. Thus, the generalizability of results is deemed to be higher compared to those of controlled clinical trials. However, due to the expected

larger range of variations in procedures and therapies the level of statistical significance is expected to be lower but allowing for generation of hypotheses which might be investigated in subsequent clinical research projects.

6.5 Monitoring plan

No routine onsite monitoring is initially planned within this non-interventional, observational study. Since only observation of routine clinical care without any protocol-defined interventions will be performed, the safety and well-being of study patients is the scope of routine clinical care. Thus, onsite monitoring could be justified for double-check of completeness and quality of data, only. Data quality will primarily be controlled by means of statistical checks on data available for all study sites allowing to detect outliers, extremes and deviation in distribution of data. In case of suspicious findings, on-site visits in corresponding sites might be performed.

7. Statistical considerations

In this observational study the time period from index therapy to release for oral food intake (in upper GI tract use) or endoscopic release for stoma relocation (in lower GI tract use) will be compared to published historic controls. For this, the time period is compared to published data of other EVAC and conventionally managed therapy, especially data from Wasmann et al. [29]. In addition, after half of the patients with complete follow-up, an interim analysis will be performed and sample size will be recalculated. It is expected that until then the results of a randomized clinical trial comparing an EVAC therapy to standard minimally invasive oesophagectomy (refer to NCT04162860 and [22]) will be available for adaptation of assumed confidence intervals and sample size (see 6.3.7). The hypothesis of superiority against conventionally managed therapy will be tested confirmatory.

For primary analysis a one-sample log-rank test will be used, comparing the observed number of events to the expected number of events of the control groups. The two-sided type-one error is 0.54% for the interim analysis and 4.92% for the final analysis.

Data from all study sites will be pooled for analysis. Standard statistical methods will be used to analyse all data. Continuous variables will be summarized using the number of observations, mean, median, standard deviation, minimum and maximum values. Categorical variables will be summarized using the number of observations and percentages.

A separate Statistical Analysis Plan will be prepared prior to the start of data analysis, detailing the statistical analyses methods that will be used.

8. Data management

Study and site management as well as data cleaning, data management and statistical analysis was delegated by the sponsor to CRI – The Clinical Research Institute, Munich, Germany, as responsible Contract Research Organisation.

Applicable national and international legal requirements for data handling and data archiving will be met. Clinical data will be collected using the web-based MARVIN system, a GCP and 21 Code of Federal Regulations (CFR) 11 compliant Electronic Data Capture (EDC) and Clinical Trial Management System (CTMS) software based on Clinical Data Interchange Standards Consortium (CDISC) data standards. Medical data within this study will be recorded directly in the e-CRF at the site without use of paper documents. The e-CRF system is available for all participants in the study 24 hours/7 days during the course of the study. Before closure of the study, all participating sites will be provided media with PDFs of all e-CRF data ever entered in the corresponding site together with all related metadata (e. g. audit trail, data queries).

8.1 Electronic case reporting form

The e-CRF has been approved by the SC. It is identical for each site and is provided in German language. Data will also be collected about the site itself (e.g. type of institution and other administrative data), and basic, pooled details about its patients in focus to allow for control of selection bias.

8.2 Personal data and data protection

All data obtained in the context of this observational clinical study are subject to data protection according to EU GDPR. This applies to patients' data as well as to investigators' personal data which may be included in any database of the sponsor or the CRO. Data protection processes and responsibilities according to EU GDPR are defined in agreements on joined control of data between study sites and the sponsor as well as in an agreement of data processing between the sponsor and the CRO.

The storage of data for statistical assessment shall likewise be performed only under the patient's study number. Only authorised staff members in each site can assign identifiers to personal data. If personal data are stored and processed, requirements for data protection will be followed. The study database is centrally stored on redundant servers in Germany provided by the e-CRF system vendor and under the control of the CRO.

All recorded data will be pseudonymised for storage in the central database during the course of the study. As the decoding information is held only by the treating study sites, nobody else will know the identity of the participating patients. After the end of the project, the data will be deleted from the vendor's servers and transferred to the sponsor where it will be stored according to regulatory requirements and sponsor's SOPs.

Data will only be collected and processed to reach the goals of the study. Personal data of the patient are demographic data (e.g. height, weight, data on comorbidities, data on current therapy), SAEs and therapy data. Data will be transferred to the CRO (database management, data cleaning, data analysis), to sponsor's subsidiaries within the EU and to the scientific SC.

The patient will be informed about the study and her/his rights in terms of data usage, data storage, correction of data and deletion of stored data.

8.3 Completion of Case Report Forms

All medical data within this study will be recorded directly in the e-CRF without the use of paper CRF. The investigator must ensure the accuracy, completeness, legibility and timeliness of data reported in the e-CRF and of all required clinical reports (e. g. in case of SAEs). Any change or correction to the data in the e-CRF must be explained as a prerequisite of the e-CRF system. Any change or correction to an e-CRF item will automatically be tracked (audit trail), recording the person logged-in as well as the time stamp of the change and the reason for change. The e-CRF system will not accept changes without given reason. The history of changes to a single item including original entries is always visible to the responsible local research team and to the CRO.

Data reported in the e-CRF that are derived from source documents should be consistent with the source documents or existing discrepancies should be explained. Upon entry into the e-CRF the data will be automatically stored in the central study database in pseudonymised form.

8.3.1 Data documented by study sites

Data will be derived from clinical routine care records and findings, observations or other sources (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes, recorded data from automated devices, patient files, laboratories and medico technical departments). In cases where data are collected while speaking to the patient, the e-CRF is the source document (if the patient's answer is documented there without prior documentation on paper).

SAEs during FU will be assessed by the treating investigator.

8.3.2 Quality control

Quality control is defined as the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the study-related activities have been fulfilled. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Quality assurance is defined as the planned and systematic actions that are established to ensure that the study is performed, and the data generated, documented (recorded) and reported, in compliance with GCP according to ISO 14155:2020 and applicable regulatory requirements.

Source Data

Source data are defined as all information obtained in clinical routine care and stored in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Source Documents

Source documents are defined as original documents, data and records in clinical routine care (e.g. hospital records, clinical and office charts, laboratory notes, memoranda or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x- rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments).

Access to Source Data/Document

The investigator will permit, and participating patients will consent for, study-related monitoring, audits, EC review and regulatory inspections, providing direct access to primary patient data (i.e. source data) that support data in the e-CRFs, i.e. general practice charts, hospital notes, appointment books, original laboratory records, etc. Because this is a patient confidentiality issue, access to such data must form part of the Informed Consent Form to be signed by the patient.

Direct Access

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of a clinical study. No identifiable patient data can be released from a site. Any party (e.g. domestic and foreign regulatory authorities, the sponsor and/or authorised representatives of the sponsor such as monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

Audits

An audit is a systematic and independent review of study-related activities and documents to determine whether the validated study-related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, designated standard operating procedures (SOP), GCP according to ISO 14155:2020 and applicable regulatory requirements. An independent audit at the site may take place at any time during or after the study.

9. Amendments to the study protocol

Amendments to study protocol will be sent to each corresponding EC. In case of substantial amendments to protocol the vote of the responsible EC is a prerequisite before coming into force for corresponding study sites. In case of non-substantial amendments to protocol modifications will be implemented as soon as the sponsor and the SC signed the document.

Regulatory bodies are not involved in this non-interventional, observational study. Thus, amendments to protocol will not be submitted to them.

10. Deviations from study protocol

Protocol deviations are any unapproved changes, deviations or departures from study design or procedures of a research project that are under the investigator's control and that have not been reviewed and approved by the SC.

This clinical study is purely observational. All procedures and therapies are performed as routine clinical care based on individual decisions by the treating physician and are not defined in the study protocol. This includes timing of procedures and follow-up visits as well as measures available for reporting which are defined as recommendations in the study protocol. Deviations from study protocol might therefore primarily occur for in- and exclusion criteria.

11. Device accountability

No investigational devices are used, thus, device accountability is not applicable.

12. Statements of compliance

This clinical study is purely observational. All therapies used are decided individually by the treating physician and are not pre-defined by the study protocol. All therapies used within this study have to be in line with their marketing authorisation, i.e. IFU.

Participation in this study does not pose additional risks or benefits compared to routine clinical practice because only data created within routine clinical care will be documented in this observational study, no study-specific interventions will be performed. All therapeutic decisions and procedures should be in accordance with routine clinical care following applicable medical, ethical and regulatory standards, e.g. ICH-GCP according to ISO 14155:2020.

No study-specific insurance is provided for patients who agree to the use of their data within this study.

Before initiating the study in a study site, a positive vote of the corresponding EC will be obtained.

This clinical study is industry funded and solely financed by the sponsor. The costs necessary to perform the study, i.e. to cover the time spent by site staff for documentation work, will be agreed upon with each investigator and will be documented in a separate financial agreement which will be signed by the site and the CRO on behalf of the sponsor, prior to the study commencing.

13. Informed consent process

All clinical data needed to evaluate the potential eligibility of a patient before study inclusion are to be performed during routine clinical care and are therefore not considered to be part of study related procedures.

A signed, EC approved informed consent form for transfer, processing and use of personal medical data, written in accordance with applicable data privacy regulations, will be obtained from every patient prior to any transfer of personal data to the e-CRF. The patient will be given sufficient time to consider the implications of consenting for transfer, processing and use of personal medical data before deciding whether to agree.

Patients undergoing the procedures of interest in this study will often be in a clinical situation requiring immediate therapy without any delay. In addition, it is expected that potential study patients might not be able to give informed consent on the use of their personal data at the time of physician's decision on the primary

intervention procedure of interest. Since this clinical study is purely observational, all therapies used are decided individually by the treating physician in routine clinical care in line with medical guidelines and the IFUs of the devices used but not pre-defined in the study protocol. Thus, informed consent for use of personal data will be given subsequent to the primary intervention procedure of interest but before any data transfer to the e-CRF.

Should there be any modifications to the protocol, such that this would directly affect the patient's consent for transfer, processing and use of their personal medical data in the study, an addendum to the informed consent form specifying the modification must be compiled and the active patients must agree to sign this addendum indicating that they also agree to the modifications within the study.

A signed copy of the patient's informed consent form must be maintained in the study file on site, a copy of the signed informed consent form must be provided to the study patient. The patient's permanent medical records should indicate the patient's study participation.

14. Adverse events, adverse device effects and device deficiencies

SAEs will be documented following ISO 14155:2020 and reported in accordance with applicable national standards. Since the study is observational, all therapies and procedures represent routine clinical care in line with applicable medical guidelines, market authorisations and corresponding IFUs. Since no risks or benefits compared to routine clinical care will be added, the rate of non-serious AEs will be identical to routine clinical care. Thus, non-serious AEs will not be documented within this study but AEs of special interest (AEoSI), only (refer to section 14.1).

14.1 Definitions

Adverse Event (AE):

Is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device. This definition includes events that are anticipated as well as unanticipated events and those occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices. A newly diagnosed concomitant disease is also considered an AE.

AE of special interest (AEoSI)

Potential complication of index therapy:

- Iatrogenic injury of the mucosa;
- Any bleeding, appearance of fistula or abscess, pneumonia, peritonitis, or mediastinitis as a symptom of the treatment;
- Occurrence of stricture / stenosis during the follow-up.

An independent CEC will review AEoSIs based on coded (pseudonymized) copies of corresponding medical files to assess if they fulfil criteria for

Serious Adverse Event (SAE):

A **SAE** is any untoward medical occurrence that

- led to death,
- led to 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
  - hospitalisation or prolongation of patient hospitalisation, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  - a chronic disease,
- led to foetal distress, foetal death or a congenital abnormality or birth defect.

More than one of the above criteria can be applicable to each event.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

NOTE:

- The index treatment itself,
- a planned hospital overnight stay in follow-up for review of index defect,
- an elective hospitalisation (e.g. surgery) verifiably planned before signing consent
- overnight survey visits (e.g. sleep lab)

are not considered as SAEs if no additional medical events occur which fulfil criteria of a SAE.

An independent CEC will review SAEs (and AEoSIs) based on coded (pseudonymized) copies of corresponding medical files to assess if they fulfil criteria for

- defect treatment complication or
- being related to defect treatment.

Life-threatening

The definition of a SAE refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

Hospitalisation

- **Hospitalisation** within this protocol is defined as inpatient care for more than one calendar day (overnight stay) for any cause. Overnight survey visits (e.g. sleep lab) are not considered “hospitalisation”.
- **Hospitalisation for therapy of index defect** follows within this protocol the definition in 6.3.1.

The investigator will document in the e-CRF for each hospitalisation if he classifies it as “for therapy of index defect”.

Because hospitalisation decisions might be subject to local practices, social considerations, bed availability, and so on, hospitalisations for SAEs will be reviewed by an independent CEC based on coded (pseudonymized) copies of corresponding medical files to assess the reason and appropriateness of each hospitalisation, i.e. whether it is “for therapy of index defect”.

14.2 Device Related Adverse Events

Within this PMCF study adverse events related to the IP will be recorded and reported.

14.2.1 Device Deficiency (DD)

DD means 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. Since the study is observational, no investigational medical product will be used but all therapies and procedures represent routine clinical care in line with applicable medical guidelines, market authorisations and corresponding IFUs. Treating physicians have to report DDs related to medical devices or therapies to the corresponding manufacturers of devices concerned. Reporting duties of manufacturers of devices used within this observational study have to follow routine procedures relevant for marketed medical devices.

14.2.2 Adverse Device Effect (ADE)

Any untoward and unintended response to a medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. It also includes any event resulting from use error or from intentional misuse of the investigational medical device. Since the study is observational, no investigational medical product will be used but all therapies and procedures represent routine clinical care in line with applicable medical guidelines, market authorisations and corresponding IFUs. Treating physicians have to report ADEs related to medical devices or therapies to the corresponding manufacturers of devices concerned. Reporting duties of manufacturers of devices used within this observational study have to follow routine procedures relevant for marketed medical devices.

14.2.3 Serious Adverse Device Effect (SADE)

Any device deficiency that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate, shall be documented throughout a clinical investigation and appropriately managed by the sponsor. Since the study is observational, no investigational medical product will be used but all therapies and procedures represent routine clinical care in line with applicable medical guidelines, market authorisations and corresponding IFUs. Treating physicians have to report ADEs related to medical devices or therapies to the corresponding manufacturers of devices concerned. Reporting duties of manufacturers of devices used within this observational study have to follow routine procedures relevant for marketed medical devices.

14.3 Recording and reporting of reportable events

The following events are considered reportable events in accordance with MDR Art. 80(2):

- any SAE that has a causal relationship with the investigational device, the comparator 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;
- any new findings in relation to any event referred to in the points above.

Since this study is observational, no investigational medical product will be used but all therapies and procedures represent routine clinical care in line with applicable medical guidelines, market authorisations and corresponding IFUs. Thus, causal relationships of events to an investigational device or procedure will not be assumed. However, irrespective of this study, treating physicians have to report AEs related to medical devices or therapies to the corresponding manufacturers of devices concerned. Reporting duties of manufacturers of

devices used within this observational study have to follow routine procedures relevant for marketed medical devices.

Information on all SAEs which occurred after start of index treatment, whether related or not related to index treatment, must be collected. The investigator should specify and report in the e-CRF the nature of the sign or symptom leading to the SAE, the date of onset of the sign or symptom, the date of resolution of the specific event (not of the underlying disease), the intensity, interventions performed (if any), the relationship to index treatment, and the outcome.

All SAEs must be reported expeditiously by the investigator to the sponsor through the SAE section of the e-CRF **within 24 hours of becoming aware of the event**. A SAE form within the e-CRF should be completed for any event where doubt exists regarding its status of seriousness. As a minimum, the investigator has to fill out the following items in the internet-based SAE form within **24 hours of becoming aware of the event**:

- Type of event
- Description
- Date of onset
- Criteria for seriousness

As soon as further information regarding the event is available, the investigator should complete the documentation in the e-CRF and sign it electronically. Copies of relevant medical documents, of reports regarding examinations carried out and/or diagnostic findings should be digitally provided to the CRO after adequate blinding of patient identifiers, only.

Follow-up of any **SAE that is fatal or life threatening** should be digitally provided immediately but no later than within **2 calendar days of becoming aware of the event.**

Any SAE reporting (initial reporting and follow-up information on e.g. changes of an ongoing SAE's intensity or relationship to the investigational product or outcome) is done through the SAE section of the e-CRF. An automated e-mail notification system within the e-trial management system will inform the CRO instantaneously, thus, no extra SAE form needs to be transmitted but the CRO will receive an automated digital notification on the SAE at the same time of the data being documented or changes of relevant SAE data being made in the e-CRF.

The investigator shall report in detail all SAEs as well as AEoSIs.

14.3.1 Definition of Intensity

Be aware that intensity of an AE and its seriousness are independent definitions, e.g. an AE might be serious but mild in intensity or vice versa.

Intensity	**Definition**
Mild	Patient is aware of signs and symptoms but they are easily tolerated
Moderate	Signs/symptoms cause sufficient discomfort to interfere with usual activities
Severe	Patient is incapable to work or perform usual activities

14.3.2 Definition of Causality

The sponsor and the investigators will use the following definitions to assess the relationship of SAEs to the index therapy (devices used and procedure itself).

Not related

Relationship to index therapy can be excluded when:

- the event has no temporal relationship with the use of the devices or the procedures;
- the SAE does not follow a known response pattern to the index therapy (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of the index therapy 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 SAE;
- the event involves a body-site or an organ that cannot be affected by the index therapy;
- the SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of other devices, drugs, treatments or other risk factors).

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.

Possible

The relationship with the index therapy 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 other devices, drugs or treatments). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable

The relationship with the index therapy seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship

The SAE is associated with the index therapy beyond reasonable doubt when:

- the event is a known side effect of the index therapy or of similar devices and procedures;
- the event has a temporal relationship with the index therapy;
- the event involves a body-site or organ that
  - the index therapy is applied to;
  - the index therapy has an effect on;
- the SAE follows a known response pattern to the index therapy (if the response pattern is previously known);
- the discontinuation of the index therapy (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 other devices, drugs or treatments) have been adequately ruled out;
- harm to the subject is due to error in the index therapy.

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.

The sponsor of the study is responsible for reporting of reportable events to regulatory bodies according to his duties in routine clinical care. No specific reporting requirements to regulatory bodies are defined within this observational study. The reporting will be done according to MDR and national laws as serious incidents (of marked medical devices) by the Person Responsible for Regulatory Compliance-Vigilance (PRRC-V) of the sponsor.

15. Vulnerable population

Patients undergoing the procedures of interest in this study will often be in a clinical situation requiring immediate therapy without any delay. In addition, it is expected that potential study patients might not be able to give informed consent on the use of their personal data at the time of physician's decision on the primary intervention procedure of interest. Since this clinical study is purely observational, all therapies used are decided individually by the treating physician in routine clinical care in line with medical guidelines and the IFUs of the devices used but not pre-defined in the study protocol. Thus, informed consent for use of personal data will be given subsequent to the primary intervention procedure of interest but before any data transfer to the e-CRF.

16. Suspension or premature termination of the study

The SC may decide discontinuation of the study if patients cannot be enrolled in sufficient numbers within a certain time period.

The sponsor in collaboration with the SC has the right to close local study sites for enrolment of further patients if data quality and completeness is out of range, if the site does not comply with the study protocol or decisions of the committees or if the site remains inactive for several months. Such decisions will always be taken on a case-by-case basis and after corresponding reminders to the local study team.

17. Publication policy

Study results will be pooled across all participating sites for the purpose of publication that will be coordinated by the sponsor. Preparation of a comprehensive publication will occur at the completion of the study, but the sponsor may, at its discretion, coordinate an additional, interim publication. The order of authorship will be determined by the sponsor and will be based in part on the number of qualified and completing patients at each site.

An investigator intending to publish results of the study must provide the sponsor with a copy of any proposed publication, abstract, or presentation at least 60 days prior to submission for publication or presentation. The sponsor will have the right to object to the publication, abstract, or presentation if, in the sponsor's reasonable opinion, such publication (i) contains confidential information; or (ii) will adversely affect any intellectual property or proprietary right of the sponsor. In the event of an objection by the sponsor, the investigator must either modify or delay the publication, abstract, or presentation for a period requested by sponsor not to exceed ninety (90) days to permit the sponsor to re-dress or mitigate risks.

Investigators and sites must acknowledge the sponsor in all publications or presentations resulting from this study and provide any required disclosures.

All relevant measures for transparency of clinical studies, and especially the recommendations of the editors of the major medical journals, will be met.

18. Bibliography

1. Ahrens, M., et al., Drainage of esophageal leakage using endoscopic vacuum therapy: a prospective pilot study. Endoscopy, 2010. 42(9): p. 693-8.
2. Arezzo, A., et al., Endoluminal vacuum therapy for anastomotic leaks after rectal surgery. Tech Coloproctol, 2010. 14(3): p. 279-81.
3. Arezzo, A, et al., Long-term efficacy of endoscopic vacuum therapy for the treatment of colorectal anastomotic leaks. Dig Liver Dis. 2015;47(4): p. 342-5.
4. Bludau, M., et al., Management of upper intestinal leaks using an endoscopic vacuum-assisted closure system (E-VAC). Surg Endosc, 2014. 28(3): p. 896-901.
5. Borejsza-Wysocki, M., et al., Endoscopic vacuum-assisted closure system (E-VAC): case report and review of the literature. Videosurgery and other Miniinvasive Techniques, 2015. 10(2): p. 299-310.
6. Brangewitz, M., et al., Endoscopic closure of esophageal intrathoracic leaks: stent versus endoscopic vacuum-assisted closure, a retrospective analysis. Endoscopy, 2013. 45(6): p. 433-8.
7. Hausen, A., et al., Erfolgreiche endoskopisch-endoluminale Vakuumtherapie von iatrogenen und spontanen Perforationen des distalen Ösophagus. Z Gastroenterol, 2015. 53(08): p. KG348.
8. Heits, N., et al., Endoscopic endoluminal vacuum therapy in esophageal perforation. Ann Thorac Surg, 2014. 97(3): p. 1029-35.
9. Keskin, M., et al., Effectiveness of Endoluminal Vacuum-assisted Closure Therapy (Endosponge) for the Treatment of Pelvic Anastomotic Leakage After Colorectal Surgery. Surg Laparosc Endosc Percutan Tech, 2015. 25(6): p. 505-8.
10. Kühn F, et al. Endoscopic vacuum therapy for the treatment of colorectal leaks - a systematic review and meta-analysis Int J Colorectal Dis 2022 Feb; 37(2): 283-292
11. Laukoetter, M.G., et al., Successful closure of defects in the upper gastrointestinal tract by endoscopic vacuum therapy (EVT): a prospective cohort study. Surg Endosc, 2017. 31(6): p. 2687-2696.
12. Loske, G. Müller, M, Vacuum Therapy of an Esophageal Anastomotic Leakage – A Case Report, Zentralbl Chir 2009; 134: p. 267–270.
13. Loske G, Schorsch T, Müller C. Endoscopic vacuum sponge therapy for esophageal defects. Surg Endosc. 2010;24(10): p. 2531-5.
14. Loske, G., et al., Spontaneous perforation of an intramural esophageal pseudodiverticulosis treated with intraluminal endoscopic vacuum therapy using a double-lumen vacuum drainage with intestinal feeding tube. Endoscopy, 2016. 48 Suppl 1: p. E154-5.
15. Loske, G., et al., Endoscopic intraluminal vacuum therapy of duodenal perforation. Endoscopy, 2010. 42 Suppl 2: p. E109.
16. Loske, G., et al., Intraluminal and intracavitary vacuum therapy for esophageal leakage: a new endoscopic minimally invasive approach. Endoscopy, 2011. 43(6): p. 540-4.
17. Loske, G., et al., Intraluminal endoscopic vacuum therapy in a case of ischemia of the blind end of the jejunal loop after Roux-en-Y gastrectomy. Endoscopy, 2014. 46 Suppl 1 UCTN: p. E575-6.
18. Loske G. Endoscopic negative pressure therapy of the upper gastrointestinal tract. Chirurg 2019; 90, 1–6.
19. Mees, S.T., et al., Endo-vacuum assisted closure treatment for rectal anastomotic insufficiency. Dis Colon Rectum, 2008. 51(4): p. 404-10.

20. Mennigen, R., et al, Comparison of endoscopic vacuum therapy versus stent for anastomotic leak after esophagectomy. Journal of Gastrointestinal Surgery, 2015, 19(7), p. 1229-1235

21. Moschler, O. and Muller, M., Endoluminal vacuum therapy for iatrogenic perforation of the proximal esophagus. Z Gastroenterol, 2014. 52(3): p. 281-4.

22. Müller, PC, et al., Pre-Emptive Endoluminal Negative Pressure Therapy at the Anastomotic Site in Minimally Invasive Transthoracic Esophagectomy (the preSPONGE Trial): Study Protocol for a Multicenter Randomized Controlled Trial. Int J Surg Protoc. 2021 Mar 18;25(1): p. 7-15. doi: 10.29337/ijsp.24.

23. Richter F. and al. Eso-Sponge® for anastomotic leakage after oesophageal resection or perforation: outcomes from a national, prospective multicentre registry, BJS Open 2022 Mar 8;6(2)

24. Schniewind, B., et al., Endoscopic endoluminal vacuum therapy is superior to other regimens in managing anastomotic leakage after esophagectomy: a comparative retrospective study. Surg Endosc, 2013. 27(10): p. 3883-90.

25. Smallwood, N.R., et al., The use of endoluminal vacuum (E-Vac) therapy in the management of upper gastrointestinal leaks and perforations. Surg Endosc, 2016. 30(6): p. 2473-80.

26. Strangio, G., et al., Endo-sponge therapy for management of anastomotic leakages after colorectal surgery: A case series and review of literature. Dig Liver Dis, 2015. 47(6): p. 465-9.

27. Turkyilmaz, A., et al., The management of esophagogastric anastomotic leak after esophagectomy for esophageal carcinoma. Dis Esophagus, 2009. 22(2): p. 119-26.

28. Wallstabe, I., et al., Endoluminal vacuum therapy for anastomotic insufficiency after gastrectomy. Endoscopy, 2010. 42 Suppl 2: p. E165-6.

29. Wasmann, KA, et al., Endo-sponge Assisted Early Surgical Closure of Ileal Pouch-anal Anastomotic Leakage Preserves Long-term Function: A Cohort Study. J Crohns Colitis. 2019 Dec 10;13(12): p. 1537-1545. doi: 10.1093/ecco-jcc/jjz093.

30. Wedemeyer J. et al Management of major postsurgical gastroesophageal intrathoracic leaks with an endoscopic vacuum-assisted closure system. Gastrointest Endosc 2010 Feb;71(2): p. 382-6.

31. Weidenhagen, R., et al., Endoluminal vacuum therapy for the treatment of anastomotic leakage after anterior rectal resection. Rozhl Chir, 2008. 87(8): p. 397-402.

32. Zhang CC, Liesenfeld L, Klotz R, Koschny R, Rupp C, Schmidt T, Diener MK, Müller-Stich BP, Hackert T, Sauer P, Büchler MW, Schaible A. Feasibility, effectiveness, and safety of endoscopic vacuum therapy for intrathoracic anastomotic leakage following transthoracic esophageal resection. BMC Gastroenterol. 2021;21(1): p. 72.

Annex 1. List of stand-alone documents

No.	Title
1.	List of study sites and principal investigators
2.	List of SC members
3.	List of CEC members

Annex 2. Milestones

Section	Tasks	Date
Draft study planning	Draft Protocol	24.07.2019
Final study planning	Final protocol	07.12.2023
Study preparation	e-TMS, e-CRF; other study relevant documentation	01.08.2022
	Start of site selection, site contacts, site evaluation	01.08.2022
	First EC submission	15.12.2023
Study initiation	Start of site contracting	15.12.2023
	Start of supply of sites with study materials, start of initiation visits	15.02.2024
	Start of recruitment period (FPI)	15.02.2024
	End of recruitment period (LPI)	14.02.2026
Study duration	End of follow-up of last patient	14.05.2026
	Median follow-up period of all patients	3 Months
Database lock	End of final data cleaning	14.06.2026
Final analysis	Results to be presented to SC	15.06.2026