This suplement contains the following items:

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A Randomized, Sham and Cross-Over-Controlled Trial of per-oral endoscopic pyloromyotomy (G-POEM) in patients with refractory gastroparesis

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Countries of recruitment: Czech Republic, Germany, Belgium, Nederland, Great Britain, Sweden, Denmark, Slovak Republic, USA, Romania.
While the study is ongoing, further centres might be included.
Commetties: (appendix 1)

ClinicalTrials.gov Identifier: NCT03356067
Date of registration:29.11.2017

Study type: Interventional
Allocation: randomized
Intervention model: parallel block assignment
Masking: sham-controlled

Date of first enrolment: December 2017
Target sample size: 86 patients

Recruitment status: Recruiting

Primary outcome(s): Improvement of Gastroparesis Cardinal Symptom Index after endoscopic intervention in patients with severe gastroparesis
Duration of follow-up: 36M

Protocol version:

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Author(s): Prof. J.M., Prof T.R

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Sources and types of financial, material, and other support.

There is no official founding for this multicenter international study and each center is responsible for its cost related to this study.

Table 1:

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2. Abbreviations:

AE – Adverse Event
sAE – serious Adverse Events
ANMS – American Nuclear Medicine Society
BI, BII – Billroth
BMI – Body Mass Index
CRP – C-Reactive Protein
DM – Diabetes Mellitus
DSMB – Data and Safety Monitoring Board
ESD – Endoscopic Submucosal Dissection
GCSI – Gastroparesis Cardinal Symptom Index
GEBT – Gastric Emptying Breath Test
GET – Gastric Emptying Study
GE – Gastric Emptying
GI – Gastrointestinal
GIST – Gastrointestinal Stromal Tumor
GLP – 1 - Glucagon Like Peptide -1
GP – Gastroparesis
G-POEM – per oral endoscopic pyloromyotomy
IE – Interim Event Report
IRB – Institutional Review Boards
PAGI-SYM - Patient Assessment of Upper Gastrointestinal Symptom severity index
PAGI-QoL – Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
POEM – Per-Oral Endoscopic Myotomy
Pyloromyotomy
POD – Post Operative Day
PPI – Proton Pump Inhibitors
RBC, WBC – Red Blood Cells, White Blood Cells
QoL – Quality of life

3. Study Summary

Gastroparesis is a disorder triggered by numerous causes and it is defined by symptoms and with an objective evidence of delayed gastric emptying in the absence of obstruction (albeit pyloric spasms may play a role in a subset of patients). Gastroparesis may be a consequence of medication, surgery or diabetes but in approximately one third of patients, the cause remains unknown and the patients are diagnosed with idiopathic gastroparesis. Effective treatment for gastroparesis is challenging especially in patients with severe symptoms. The efficacy of prokinetics is dubious since they have not proven real clinical efficacy in placebo-controlled trials. In refractory gastroparesis, endoscopic or surgical treatments may therefore be considered. Endoscopic treatments include intrapyloric injection of botulinum toxin and transpyloric insertion of a metallic stent. Surgical options involve implantation of a gastric „pacemaker“ (gastric stimulation), pyloroplasty and subtotal gastrectomy. The partial effectiveness of botulinum toxin injection, stents and pyloroplasty suggests that disruption of the pyloric muscle may lead to a decreased intrapyloric tone and consequently to a symptomatic improvement in some patients with refractory gastroparesis.

Recently, a new endoscopic technique, gastric endoscopic per oral pyloromyotomy (G-POEM) has been introduced with promising preliminary results. Uncontrolled studies with so far limited number of patients have demonstrated a significant symptomatic improvement in approximately 70% of patients and improved or normalized of gastric emptying in more than a half of patients after G-POEM. A prospective uncontrolled study suggested that patients with idiopathic or post-surgical gastroparesis experiences higher success rate after G-POEM (70-80%) compared to patients with diabetic gastroparesis (50%).

G-POEM is, in principle, adaptation of POEM (per-oral endoscopic myotomy) in the stomach. POEM is now considered a standard treatment for esophageal achalasia and it has been shown to be safe and effective. In contrast to achalasia, pathophysiology of pyloric function in patients with gastroparesis is less understood and the explanation of how and why G-POEM should work is some-how hypothetical. For example, presumed pylorospasm has not been demonstrated as the predictive factor for treatment success of G-POEM yet. Refractory gastroparesis is often accompanied by psychological or even psychiatric disturbances and hence a placebo“ effect of G-POEM cannot be ruled out. Therefore, the real clinical efficacy of G-POEM can only be demonstrated in a clinical randomized sham-controlled trial.

To assess the severity of gastroparesis-related symptoms, the Gastroparesis Cardinal Symptom Index (GCSI) has been developed for this item. The GCSI is part of a larger questionnaire PAGI-SYM (Patient Assessment of Upper Gastrointestinal Symptom severity

index) established for assessment of patient-reported symptoms in gastroparesis (dyspepsia and gastroesophageal reflux) [1]. PAGI-SYM as well as GCSI subscale scores varied significantly by global disease severity, with higher (worse) scores observed in those subjects who rated their gastroparesis as moderate to severe.

The aim of this prospective, sham-controlled, cross-over study (cross-over for patients randomized to the sham arm) is to compare short and long-term efficacy and safety of G-POEM in patients with refractory gastroparesis. Symptoms and objective parameters of gastric emptying will be the main outcome criteria. The reason of using a sham protocol is to control for the potential confounders (therapeutic effects of touch and belief, which are components of the placebo effect**).**

We plan to randomize 86 patients (43 in the active arm, ratio 1:1 active vs. sham). Sample size is calculated based on expected therapeutic success of G-POEM in 50% of patients vs. 20% in the sham group; significance level 0,05; study power 0,8; beta error 0,2; adjustment for 15% expected drop out.

Patients will be randomized in blocks of 6, stratified according to the etiologies: (idiopathic, diabetic, and post-surgical; patients after esophagectomy with gastric pull-through will not be included). Control visits will be scheduled at 3, 6, 12, 24, and 36 months. The primary outcome will be the proportion of patients with treatment success in the active group vs. sham group at 6 months after the procedure. Several secondary outcomes will also be assessed, including procedure-related parameters and safety parameters and change in Gastric Emptying Study (GET) after G-POEM vs. sham. After 6 months, patients randomized to the sham group will be offered G-POEM procedure and further followed up (cross-over part of the study) providing that they did not have a therapeutic effect of the sham procedure.

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4. Introduction

Gastroparesis (GP) is relatively common gastrointestinal (GI) motility disorder, defined as epigastric symptoms associated with delayed gastric emptying (GE) in the absence of a mechanical obstruction. The prevalence of gastroparesis is unknown due to the difficulties inherent of undertaking true population-based studies. In a large study, the age-adjusted incidence of gastroparesis was 2.4 per 100,000 person-years for men and 9.8 per 100,000 person-years for women [2]. Women are more commonly affected than men [3]. In clinical practice, idiopathic and diabetic gastroparesis are the most common causes, each accounting for about one third of the patients [4]. While traditionally gastroparesis has been mainly associated with type 1 DM, the global rise of obesity-related diabetes has resulted in a high proportion of gastroparesis patients with type 2 DM. The cumulative incidence of developing gastroparesis in type 1 DM is 5.2% over 10 years and 1% in type 2 DM. Gastroparesis may also develop as a consequence of gastric or abdominal surgery or may accompany some other neurological, infectious, and infiltrative disorders [4-7]. Symptoms are not specific and may be mild, moderate or severe and include nausea, vomiting, dyspeptic symptoms, regurgitation, weight loss and poor nutritional status.

Diagnosis of gastroparesis should be confirmed by an objective gastric emptying study. Gastric scintigraphy has been considered as the gold standard for the evaluation of gastric emptying. The most reliable parameters for diagnosis of gastroparesis is gastric retention of solids at 4 h after standardized food ingestion and a half-time (T1/2) of gastric evacuation [8]. More recently, Gastric Emptying Breath Test (GEBT) has been validated for the diagnosis of delayed gastric emptying, and has gained increasing acceptance now that FDA has approved gastric emptying breath test [9].

Effective treatment for gastroparesis is a real clinical challenge especially in patients with severe symptoms. Dietary measures and drugs (prokinetics, antiemetics etc.) have limited efficacy [10, 11]. If conservative measures do not help (= refractory gastroparesis), endoscopic or surgical therapies may be considered with the main aim to decrease the tonus of pyloric sphincter. Two endoscopic methods have been studied: (1) intrapyloric botulinum toxin injection is only partially effective [12, 13], and a systematic review did not confirm its clinical effectiveness compared to placebo [14]; (2) trans-pyloric stent placement may be effective but it provides only a short-term effect (stent must be removed and eventually re-inserted), and there is a considerable risk of migration [15, 16].

The surgical method of choice for treatment of refractory gastroparesis is a laparoscopic pyloroplasty according to Heineke-Miculicz [17, 18]. Two studies reported symptomatic

improvement in more than 80% of patients; however there is a risk of dumping syndrome after pyloromyotomy [16]. A longstanding experimental approach for treatment of refractory gastroparesis represents gastric stimulation, but in spite of almost 2 decades of research, the benefit of this method is still controversial [19, 20].

Traditionally, gastroparesis has been considered as a disorder caused by gastric hypomotility and the role of pyloric muscle might have been underestimated. However, recent studies have shown that pyloric pressure is elevated in a subset of patients with gastroparesis and, therefore, a pylorospasm may be an underlying cause (or an additional pathophysiological factor) of delayed gastric emptying [21]. Treatments targeting the pyloric muscle leading to its decreased tone may therefore provide a therapeutic effect.

In 2007 Pasricha et al. published experimental endoscopic esophageal myotomy by using a submucosal tunnelling technique [22]. In 2008, prof. Inoue performed the first human per-oral endoscopic myotomy (POEM) in a patient with achalasia. At present, POEM is considered as a standard treatment modality for esophageal achalasia [23-25].

Based on favourable experiences with POEM, it is conceivable that "gastric modification of POEM", so called G-POEM (gastric per-oral endoscopic pyloromyotomy), may be beneficial in patient with refractory gastroparesis. Khashab et al. performed the first human G-POEM in one patient with severe gastroparesis with a significant symptomatic improvement [26]. A French group reported promising results of G-POEM in 23 patients. In this study, G-POEM was effective (symptomatic improvement in 70% of subjects) and safe (no serious adverse events). Patients with responded to G-POEM seemed to be more effective in patients with idiopathic or post-surgical gastroparesis compared to patients with diabetic gastroparesis. (). Another multi-centre analysis of 30 patients also showed promising results of G-POEM in patients with refractory gastroparesis [26]. Thus, endoscopic pyloromyotomy seems promising mini-invasive method for the treatment of (at least some) patients with severe refractory gastroparesis. However, larger studies comparing this new method with other treatment modalities or with a "sham" procedure are necessary to establish a real potential of G-POEM for treatment of this disease.

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5. Hypothesis & specific aims

This study intends to assess the clinical efficacy and safety of G-POEM in patients with refractory gastroparesis in a randomized, cross-over, sham controlled trial.

The null hypothesis to be tested (refused): G-POEM has the comparable efficacy to the sham procedure in patients with refractory gastroparesis.

6. Methods

6.1 Patient recruitment, in- and exclusion criteria

Patients will be prospectively recruited from all participating centres. Inclusion and exclusion criteria are listed in Table 2. All main etiologies of gastroparesis are eligible for enrolment (e.g. idiopathic, diabetic and post-surgical).

Table 2: In- and exclusion criteria

Inclusion criteria:	
1	**Refractory** (> 6 months) and severe (based on a validated total GSCI = Gastroparesis Cardinal Symptom Index) gastroparesis, with confirmed gastric emptying based on a gastric emptying study: standardized protocol of **scintigraphy in all patients** (performed less than 6 months prior to enrolment), or confirmed by a **validated gastric emptying breath test** [27]. The total GSCI score must be >2.3 [28]. • Abnormal gastric emptying is defined as retention of Tc-99 m >60% at 2 h and/or ≥10% of residual activity at 4 h on a standardized sulphur colloid solid-phase gastric emptying study. • Radiolabelled liquids emptying study will be reserved as alternative technique for patients with poor tolerance of solids during scintigraphy. Abnormal gastric emptying will represent >50% retention of radiolabelled content (e.g. In-111) at 1 hour. • Abnormal gastric empyting breath test based on a solid normal range determination for the test used (e.g. T1/2 > 109 min)
2	Severe refractory disease is defined as GCSI >2.3 and failure or recurrence in patients who received available optimal pharmacological therapies.
3	Persons 18 years or older at the time of signing the informed consent
4	Signed informed consent

Exclusion criteria	
1	No previous attempt with at least one prokinetic drug
2	No previous attempt to withdraw anticholinergic agents and glucagon like peptide -1 (GLP-1) and amylin analogues* in patients treated with these substances
3	Active treatment with opioids or a history of treatment with opioids within 12 months before enrolment.
4	Previous gastric surgery BI or II, esophagectomy, gastric pull-through
5	Previous pyloromyotomy or pyloroplasty
6	Known eosinophilic gastroenteritis
7	Organic pyloric (or intestinal) obstruction (fibrotic stricture, etc.)
8	Sever coagulopathy
9	Esophageal or gastric varices and /or portal gastropathy
10	Advanced liver cirrhosis (Child B or Child C)
11	Active peptic ulcer disease
12	Pregnancy or puerperium
13	Malignant or pre-malignant gastric diseases (dysplasia, gastric cancer, GIST): patients with a history of such disease after its cure are eligible for enrolment
14	Any other condition, which in the opinion of the investigator would interfere with study requirements
15	Uncontrolled diabetes mellitus
16	Diagnosis of rumination syndrome or "eating" disorder (mental anorexia, bulimia nervosa) **
17	Severe constipation without using laxatives
18	Inability to obtain informed consent

* Attempts to normalize glycaemic control using amylin analogues (e.g., pramlintide) or GLP-1 analogues (e.g., exenatide) may result in delayed gastric emptying [8].

***** The presence of a rumination syndrome or eating disorders (anorexia nervosa, bulimia) is an exclusion criterion. In case of doubts, a psychiatric examination should be performed***

6.2 Questionnaire(s) (Appendix 2)

Patients will be asked to complete validated questionnaires throughout the study to assess severity of symptoms related to gastroparesis.

6.2.1 GCSI score

The GCSI consists of nine items and three subscales to measure symptoms related to gastroparesis [1]. **The nausea/vomiting subscale** consists of the following three items: nausea, retching, and vomiting. **The postprandial fullness/early satiety subscale** consists of the following four items: stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite. **The bloating subscale consists of the**

following items: bloating and stomach or belly visibly larger. The GCSI total score is constructed as the average of the three symptom subscales.

6.2.2 PAGI-SYM score

Questionnaire was developed to measure specific symptoms of patients with upper gastrointestinal disorders. It records 20 symptoms (6 subscales) and assesses their severity within the 2 weeks prior to the test. Subscale scores are calculated by averaging across items comprising the subscale; scores vary from 0 (none or absent) to 5 (very severe). The PAGI-SYM subscale scores have good internal consistency and test-retest reliability [29].

6.3 Pre-procedure tests and process

6.3.1. Prior to randomization

- Detailed history and physical examination, checking for inclusion and exclusion criteria, baseline GCSI score, PAGI-SYM and score. There is no washout period for prokinetics or antiemetics prior to G-POEM (allowed drugs). All prokinetics should be discontinued at least 48 – 72 h before gastric emptying study. Patients with a previous attempt(s) of pyloric balloon dilatation, temporary stenting or botulinum toxin injection are eligible for inclusion, but there must be a wash-out period of at least 6 months prior to randomization.
- Upper GI endoscopy with gastric and duodenal biopsies (diagnosis of *H. pylori* and exclusion of eosinophilic gastroenteritis) (less than 4 months prior to randomization). *In patients tested positive for H.pylori, its treatment will be discussed with the patient individually. Treatment of H.pylori is not necessary before enrolment unless there is an absolute indication for its treatment.*
- Gastric emptying study (**Appendix 3**): scintigraphy protocol in all patients – (protocol endorsed by ANMS: American Nuclear Medicine Society, 2009); (less than 6 months prior to randomization). *Test will begin with patients under fasting conditions for a minimum of 6 hours. A radiolabelled meal will be prepared by adding 0.75 mCi ^{99m}Tc-sulfur colloid into 2 the liquid egg whites.Eggs will be cooked in a microwave or on a hot nonstick skillet, the egges will be stirred once or twice during cooking until firm – to the consistency of an omelette. Then, the bread will be toasted and jelly spread on the toasted bread. Gamma camera images will be obtained immediately after meal ingestion and then at 1, 2, 3 and 4 hours. The geometric mean of delay-corrected counts will be used to estimate the proportion of ^{99m}Tc emptied at each time point. Diagnostic criterion for gastroparesis is defined as the percentage of gastric retention >60% at 2 h and equal to or greater than 10% at 4 h or both. Half-time (T1/2) emptying time will also be calculated. In case of poor tolerance of solids during gastric scintigraphy, radiolabelled liquids will be used (see inclusion criteria). At least 72 hours before gastric emptying test, narcotics and other medications that can delay gastric emptying should be discontinued*.

Other alternative meals may be used for patients with egg allergies or egg´s intolerance according to the local principles.

- (Optional) Gastric Emptying breath test (GEBT) (**Appendix 3**). *The kinetics of appearance of ^{13}C in breath CO2 reflects the rate of gastric emptying of the solid phase of a meal. A dose of 100 mg Octanoic Acid is administered orally in a solid test meal. The test meal is standardized and consists of one scrambled egg with two slices of white bread and 5g of margarine, together with 150 ml water (swallowed immediately after ingestion of the meal). The total caloric content is 250 kcal. The half emptying time and the lag phase time are calculated as well as the gastric emptying coefficient (GEC) (Tab 3 and 4).*

Table 3: Summary of GEBT

	Dose	Samples	
Adults	100 mg (1-^{13}C)-Octanoic Acid	2	*Before administration*
		6	*Every 5 minutes for the first 30 minutes after administration (0.5.h)*
		14	*Every 15 minutes for the next 210 minutes after administration (3.5 h)*

Normal/abnormal values of gastric empyting breath test will be based on a solid normal range determination for a test, which will be used (for example, one criterion might be a gastric emptying half-time – T1/2 > 109 min)

Table 4: FDA accepted **r**eference range cut-off points in healthy population for GEBT (https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110015c.pdf)

Time point	kPCD (min^{-1})
45 min	12.9
90 min	26.9
120 min	**34.4**
150 min	39.5
180 min	43.0
240 min	**35.0**

([i]kPCD - a metric which expresses a subject's $^{13}CO2$ excretion rate at each measurement time)

6.3.2. Randomization

Patients fulfilling all inclusion criteria (and without exclusion criteria) will be asked to sign an informed consent form. Then, participants will be randomly allocated into the two groups:

A. Group that will receive G-POEM (active arm), or
B. Group that will receive sham procedure ("placebo" arm)

The patients will be stratified by the etiology of gastroparesis and gender. Patients will be randomised in blocks of 6. After signing an informed consent form, each centre will e-mail patient initials, birth date, patient´s gender and etiology of gastroparesis (1= idiopathic or other, 2= diabetic; 3 = post-surgical) to a study nurse in Prague and she will send back as soon as possible the treatment allocation with patient´s number. Patients will be randomized in 1:1 allocation ratio and patients must not be informed about their assignment.

6.3.3. Post-randomization tests (before the procedure)

- PAGI - QoL (**appendix 4**)
- Body weight/BMI, ASA physical status
- Current lab values (Haemoglobin, WBC, RBC, Thrombocytes, CRP, Quick, Haemoglobin A1c in patients with DM)
- Upper GI endoscopy 1 day prior to the procedure (optional – for removing food residues)
- EndoFLIP measurement of pyloric distensibility, cross-sectional area and diameter – under general anesthesia before G-POEM/sham

Patients will be admitted to the hospital one day prior to the procedure or the day of the procedure. The day before the procedure, patients will be allowed to drink until 20.00. In the morning (day of the procedure), proton pump inhibitor (PPI) (e.g. omeprazole 40 mg) will be administered intravenously to patients allocated to the active (G-POEM) group; patients in the sham arm will be given placebo (normal saline) (**Appendix 5**).

7. EndoFLIP

EndoFLIP (= Functional Lumen Imaging Probe) is a new method using a principle of impedance planimetry allowing to measure distensibility of a hollow organ, ideally sphincter. In the stomach, it could help to understand the contributing pathophysiology of an impaired function of a pyloric sphincter in patients with gastroparesis. Furthermore, it could help to select appropriate patients for pylorus-directed therapies in patients with gastroparesis, as EndoFLIP provides real-time and dynamic information on pyloric distention, cross-sectional area and diameter.

EndoFLIP measurement will be performed three times: before the procedure (during sham procedure or just before G-POEM), immediately after G-POEM and 3-9 months after G-POEM, always in sedated patients (3-9 months) or in patients under general anesthesia (prior to and after G-POEM). After the calibration, the balloon, equipped with pressure and impedance sensors, will be introduced into the esophagus and under endoscopic control will be passed through the pylorus into the correct position. If necessary, special accessories (snare, grasper) will be used. After that, measurement of various parameters will be performed and the following values will be recorded: distensibility, balloon pressure, cross sectional area, diameter under different balloon volumes (30, 40 and 50 mL). EndoFLIP procedure prolongs the endoscopic examination by approximately 10-15 minutes.

G-POEM procedure

The procedure consists of the following steps (Table 5):

Table 5:

1) Mucosal incision at the greater curvature 3-5 cm from the pylorus
2) Submucosal tunnelling
3) Finding pyloric sphincter
4) Myotomy (2-3 cm) of the pyloric muscle
5) Incision closure (endoclips or suture device)

All procedures will be performed by an experienced endoscopist under general anaesthesia with a high-definition endoscope, fitted with a plastic distal attachment. Exclusively CO^2 will be used for insufflation. Submucosal tunnel will be created by choosing an entry point (usually at 5-6 o´clock) in the antrum at the greater curvature approximately 3-5 cm proximal to the pylorus. After a mucosal incision (1-2 cm), a submucosal tunnel towards pyloric muscle will be created. After finding pyloric arc, the muscle will be myotomised (at 6 o´clock position, complete myotomy to the serosa, length 2-3 cm). For the whole procedure, TT knife or IT knife (Olympus) will be used. For mucosal incision, endocut mode will be used; for tunnelling and myotomy, spray or swift coagulation will be used. Coag-grasper will be used for haemostasis. At the end of the procedure, the mucosal incision will be closed by using endoclips, alternatively, suturing device (Apollo® OverStitch), OTSC clip or KING closure (endoloop + clips) may be used at the direction of an investigator. Inadvertent mucosal injuries will be closed by endoclips if necessary. All procedure-related instruments are listed in Table 6.

Table 6: G-POEM baseline instruments

Erbe Vio 300D with presets: Endocut Q, Spray Coagulation 40-60W, Effect 2 (incision, dissection and myotomy) or Swift Coagulation. Endocut I, Spray or Forced Coagulation 40W, Effect 2 (bleeding control with coag grasper)
CO_2 Unit, low flow CO_2
Waterjet pump with sterile fluid for flushing
High definition endoscope
Single use endotherapeutic instruments: - IT and/or TT knife (with jet function if available) - Coagrasper for haemostasis - Injector - Clips or endoscopic suturing device or endo-loop device or OVESCO clip - e.g. MH-588 distal attachment (Olympus or Fuji)

Experienced endoscopist to be eligible to perform G-POEM in this study:

- At least 4 G-POEMs and one of following (Table 7)

Table 7:

A) >35 POEMs or
B) >30 ESD procedures

8. SHAM procedure

Patients randomized into the sham group will undergo general anaesthesia (or deep sedation with propofol) and a standard upper GI endoscopy with a high definition endoscope will be performed. EndoFLIP measurement will be performed during the sham procedure. No G-POEM will be effectuated and patient will be awakened after 30-60 minutes. All other post-procedure tests will be done in the same fashion as in patients with G-POEM arm.

All "trialists" including the "paramedics" staff will be asked not to inform the patient about the treatment allocation.

9. Perioperative and post-operative management and follow-up

a. Perioperative management

- Sixty to fifteen minutes before the procedure, the patients (active group) will be administered antibiotics i.v.: Ceftriaxone 2 gr (or similar antibiotics) plus Metronidazole 500 mg. Patients in the sham group will be given placebo (normal saline).
- If necessary, pneumoperitoneum will be decompressed by using a Verres needle or venous cannula.

b. Postoperative management - day of the procedure:

- Recovery from general anaesthesia/sedation
- Analgesic and anti-emetic as needed
- i.v. omeprazole 3x40 mg (or other IPP) only in active arm, placebo (normal saline) in the sham arm
- Nothing per mouth until POD 1 (both arms)
- Thorough monitoring until POD 1

c. Post-operative day 1 (POD 1):

- Morning: last dose of i.v. omeprazole 40 mg i.v. (or similar PPI) – placebo in the sham group. Then esomeprazole 2x40 mg (or other PPI) for at least 3 weeks (both arms).
- Ceftriaxone 2 gr i.v. or similar ATB, placebo in sham arm
- Blood (Haemoglobin, RBC, WBC, CRP, etc.)
- Mucosal integrity will be confirmed with either endoscopy or X-ray with water soluble contrast or both at the discretion of an investigator. *If necessary, additional intervention to close mucosal incision will be used.*
- If no leak is detected, patients will be allowed to drink clear fluids and begin re-alimentation.
- Discharge possible on POD 1 (or POD 2)

d. Follow-up visits:

Follow up visits are scheduled at 3 and at 6 months. At 6 months, all patients will be informed about their treatment allocation and patients in the sham group will be offered G-POEM in case of their persisting symptomatology (no or minor benefit of the sham procedure). The decision must be made in next 3 months and these patients undergo the G-POEM procedure no longer than 6 months after the previous follow-up visit. Further follow-up visits for patients randomized to the active arm are scheduled at 12M, 24M and 36M.

Patients originally randomized into the sham arm, who will undergo G-POEM, will be followed like patients after G-POEM (f-u visits at 3M, 6M, 12M, 24M and 36M) (**Appendix 6**) except of scintigraphy/GEBT at 12M (Table 8B).

Patients originally randomized into the sham arm who had treatment success or didn´t want to undergo G-POEM will be followed at 12M and 24M to be sure there is none treatment recurence.

For both, active and SHAM groups, diet modification, nutrition support, prokinetics, antiemetics are allowed during the follow-up. No interventions such as pyloric balloon dilatations, transpyloric stent placement, botox application or surgery) are allowed during the follow-up.

Unscheduled visits or telephone contacts may occur as needed. No time windows or minimum time separations are imposed for such visits or contacts. Data collection forms are

not required at interim visits. If gastroparesis symptom exacerbation occurs between scheduled visits, complete the Interim Event Report (IE) form. The visit code for the form will be "n" (*not applicable in this situation)*

3M visit (±3 weeks):

- Symptom questionnaires (PAGI-QoL, GSCI, PAGI-SYM)
- Body weight/BMI
- Endoscopy
- Gastric emptying study (scintigraphy) in all pts
- Gastric emptying breath test (optional)
- EndoFLIP measurement (only after G-POEM, may be performed 3-9 months after G-POEM), patients from sham group will undergo the "sham EndoFLIP measurement"

6M visit (± 1 month):

- Symptom questionnaires (PAGI-QoL, GSCI, PAGI-SYM)
- Body weight/BMI

12M visit (± 1 month):

- Symptom questionnaires (PAGI-QoL, GSCI, PAGI-SYM)
- Body weight/BMI
- Endoscopy (optional)
- Gastric emptying study (scintigraphy) in the active arm only (Tab. 8A)
- Gastric emptying breath test (optional)
- No GES (scintigraphy) in the sham group after unblinded allocation to G-POEM (Tab. 8B)

24M and 36M visit (±2 months):

- Symptom questionnaires (PAGI-QoL, GSCI, PAGI-SYM)
- Body weight/BMI
- Gastric emptying study (scintigraphy) at 36M (optional)

Table 8A – study design for patients in the active (G-POEM) group

	Patients in G-POEM group at the beginning of randomisation							
	Baseline	*POD 0 – day of GPOEM*	*POD 1*	*3M*	*6M*	*12M*	*24M*	*36M*
Scinti / GEBT	☻			☻	-	☻		☻ (optional)
Endoscopy	☻	☻	☻ (optional)	☻	-	☻ (optional)		
GCSI + PAGI-SYM + PAGI-QoL	☻			☻	☻	☻	☻	☻
Blood tests	☻		☻					
EndoFLIP		☻ *Before and after GPOEM*		☻				

GEBT (Gastric emptying breath test), QoL = Quality of Life, GCSI = Gastroparesis Cardinal Symptoms Index, PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders Symptoms, PAGI-QoL = Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life, POD – Post Operative Day.

Table 8B – study design for patients randomized in the sham group

	Patients in sham group / allocation to G-POEM procedure*											
	Baseline	*POD 0*	*POD 1*	*3M*	***6M ****	*POD 0/ **G-POEM***	***POD1***	*3M*	*6M*	*12M*	*24M*	*36M*
Scinti / GEBT	☻			☻	-			☻				☻ (optional)
Endoscopy	☻	☻	☻ (optional)	☻	-		☻ (optional)	☻		☻ (optional)		
GCSI + PAGI-SYM + QoL, PAGI-QoL	☻			☻	☻			☻	☻	☻	☻	☻
Blood tests	☻		☻				☻					
EndoFLIP		☻ *Before*[⊥]		☻ *sham*		☻ *After GPOEM*		☻				

** At 6M, the patients in sham arm will be offered to undergo G-POEM (if their symptoms persist).*
[⊥] In patients having undergone EndoFLIP during the sham procedure, no EndoFLIP measurement will be repeated prior to G-POEM.
♦ sham measurement

10. Study outcomes

a. Main outcome

Main outcome is the proportion of patients with treatment success at 6 months after the procedure.

Treatment success is defined as a decrease of a total GSCI symptom score at least **50%** (see Table 9 for GSCI values to define treatment success according to a baseline GSCI value).

Table 9: GSCI values to define treatment success according to the baseline GSCI value

Mean GCSI score total – baseline	Maximal GSCI score for treatment success (decrease of GSCI about 50%)
2.31*	1.15
2.4	1.20
2.5	1.25
2.6	1.30
2.7	1.35
2.8	1.40
2.9	1.45
3.0	1.50
3.1	1.55 (see description below the table)
3.2	1.60
3.3	1.65
3.4	1.70
3.5	1.75
3.6	1.80
3.7	1.85
3.8	1.90
3.9	1.95
4.0	2.00
4.1	2.05
4.2	2.10
4.3	2.15
4.4	2.20
4.5	2.25
4.6	2.30
4.7	2.35
4.8	2.40
4.9	2.45
5.0	2.50

NOTE: GSCI above 2.3 is an inclusion criterion

Example: If baseline GSCI value was 3.1, a patient will have treatment success if post-treatment GSCI score will be 1.55 or lower.

10.2. Secondary outcomes:

1. Proportion of patients with treatment success in the active arm at 3M, 12M, 24M and 36M.
2. Proportion of patients with treatment success in the sham group at 3M.
3. Change in GSCI and PAGI-SYM before and after G-POEM at 3, 6, 12, 24 and 36M and before vs. after sham procedure at 3M and 6M; comparison of the change of the scores between the active and sham groups.
4. Proportion of patients (randomized into the sham group and undergoing G-POEM after 6M) with treatment success after the sham procedure (6M) and after G-POEM (6M) – cross over part
5. Change in GSCI and PAGI-SYM before and after G-POEM vs. sham procedure in patients randomized to the sham group at 3 and 6M (cross over part)
6. **Subgroup post-hoc analyses of the treatment success and change in symptomatic scores according to etiology of gastroparesis.**
7. Change in gastric emptying (scintigraphy) study, EndoFLIP values and/or gastric emptying breath test before and after both G-POEM and sham procedure; comparison of the mean change of these parameters between active and sham groups.
8. Procedure details (length of the procedure, technical success, perioperative adverse events).
9. Short- and long-term adverse events**.**

11. Sample size calculation

A total of 86 patients will be randomized.

- 43 patients will be randomized into the G-POEM group
- 43 patients will be randomized into sham group

Sample size calculation is based on expected therapeutic success of G-POEM in 50% of patients vs. 20% in the sham group; significance level 0,05; study power 0,8; beta error 0,2; adjustment for 15% expected drop out.

12. Statistical analysis

Data will be analyzed for both the intention to treat (ITT – a cohort for primary end point analysis) and the per-protocol population (sensitivity analysis). The per-protocol analysis will include only patients who will complete the entire follow-up. The efficacy of G-POEM at month 6 (main outcome) will be evaluated by Poisson regression with robust standard errors or similar regresion based approach. Baseline characteristics will be compared by using chi-squared tests for categorical variables and t-tests for continuous data.

The efficacy of treatment at other time points (3M, 12M, 24M and 36M) as well as the pooled efficacy cross-over + active groups will be evaluated similarly.

Mean changes in the GCSI score and gastric emptying time in the active vs. control group will be analysed by ANCOVA. A p value less than .05 will be considered statistically significant. **An interim-analysis** will be performed when **40%** of patients will have completed the 6 months follow-up.

Statistical analysis plan

To prevent possible bias caused by the choice of statistical methods, this extended statistical analysis plan aims to adhere to the plan presented in the original version of the protocol while adding details of the planned analysis approaches.

The cohort for the primary analysis will be the intention to treat (ITT) population including all randomized patients according to their original allocation regardless of the actual treatment received or follow-up adherence to the protocol exhibited. Missing data in the ITT population will be imputed using the multiple imputation method. Further, the primary outcome will be analyzed on the per-protocol population to asses sensitivity.

The difference in efficacy of G-POEM versus sham at month 6 (main outcome) will be evaluated by logistic regression, same as the differences in treatment success at other time points (3M, 12M, 24M and 36M). Logistic regression will also be used to search for predictors of treatment success among other variables (age, sex, baseline values of scores, baseline GES, and EndoFLIP measurements).

Further, 95% confidence intervals for the point estimates of treatment success rates will be constructed using the Wilson method for G-POEM, sham, cross-over, pooled original + cross-over G-POEM groups and also etiology sub-groups at all time points.

Continuous secondary outcome variables will be presented as means or medians with 95% confidence intervals in dependence on the results of normality test for particular variables. The confidence intervals will be constructed using a bootstrapping method, which can be

conveniently combined with the multiple imputation approach even for estimation of the median, where normality is not assumed. Between group differences for the secondary outcomes will be tested using t-tests, possibly after data transformation for highly non-normal data.

The difference in treatment success between G-POEM and sham groups at 6 months is the only confirmatory hypothesis test of the study and the 5% p-value threshold for statistical significance will be applied. All the other hypotheses and secondary outcomes are considered exploratory and p-values from the corresponding tests will be presented without any multiple testing correction without the aim to keep the overall false positive error rate at 5% across all results.

Baseline characteristics will be compared only using descriptive statistics as any potential statistically significant difference between the two study groups would be due to chance by design in a randomized trial.

An interim-analysis will be performed when 40% of patients will have completed the 6 months follow-up. The interim analysis will be performed on available data basis investigating the primary hypothesis with the same tools as planned for the final analysis. Since no rules for interim stopping of the trial based on adjusted thresholds for p-values was specified in the study design, the Haybittle–Peto boundary will be used for potential stopping of the trial for early confirmation of the treatment effect. On the other hand, enrollment would be stopped for futility if the interim conditional power of the study assuming the observed effect sizes for the remaining patients was below 20%. Also, analysis of adverse events could result in study termination.

13. Study monitoring, data and safety monitoring board

The study will be monitored by an independent certified agency (to check for reliability of data and ethical standards). A standard Data and Safety Monitoring Board (DSMB) will be created in the coordinating centre in Prague and its membership will include: 4 gastroenterologists, 1 independent specialist (MD), 1 statistician, 1 lawyer and 1 independent person (not MD). The main aim of DSMB will be: to review the research protocols, informed consent documents, and plans for data and safety monitoring, including all proposed revisions; to evaluate the progress of studies, including periodic assessments of data quality and timeliness, participant recruitment; to protect the safety of the study participants; to report on the safety of the study participants and progress of the trial; to consider factors external to the study when relevant information becomes available, such as scientific or therapeutic

developments that may have an impact on the safety of the participants or the ethics of the study; to make recommendations.

14. Study termination

Individual case:

- *Severe peri-procedural complications as bleedings or perforations requiring a surgical intervention.*
- *Technically unsuccessful/unfinished G-POEM.*
- *The patient's request to terminate the participation in the study.*
- *Severe symptomatology requiring intervention not allowing to finish 6 months of the follow up, especially in patients in the sham group (pyloric botulinum toxin injection, balloon dilatation, laparoscopic surgery, transpyloric stenting).*

15. Ethical and administrative aspects

15.1. Ethical considerations

The study will be conducted according to the Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 59th WMA General Assembly, Seoul, October 2008. Approval of the medical ethical committee or Institutional Review Board of all participating centers will be obtained. The DSMB in Prague (see above) will function as independent safety monitoring board and will receive written study reports of study outcomes and follow-up. All patients are required to sign a written informed consent form prior to randomization. Study patients can leave the study at any time for any reason without consequences. The study protocol, patient information and informed consent form and all other necessary documents (study amendments) will be submitted together with an appropriate request form to Ethical Committees (or IRB) for approval at each participating centre.

15.2. Patient Information and Informed Consent

Each patient will be informed adequately about content, consequences and risks of the study. This will happen by a standardized consent form, as well as verbally by a study investigator at each centre. It is the responsibility of the principal investigator or his assigned co-investigators to obtain signed informed consent according to the international standards

(including data management and security) from each patient before inclusion into the study. Patients will be given the opportunity to ask any questions that might arise. The informed consent form will be filled single-handed by the patient. The original remains at the study site, the patient will be handed a copy.

15.3. Data security

Only anonymous data will appear in any publication. Regulations of data security of the countries of the participating centres will be adhered to. Patients will be informed that their data will be pseudonymized according to documentation obligations and notification duties by §§ 12 and 13 GCP enactment. Patients who will not agree with these regulations will not be enrolled. Patients will be provided with a code during the randomization process. For data management, only pseudonymized data will be provided to the main study centre (Prague).

15.4. Administrative Aspects and Adverse Events recording

Patients will be coded using a numeric randomization code (anonymized) and only anonymized data will be submitted to the PI site (Prague) for data management. Adverse events (AE) and serious adverse events (SAE) (**Appendix 8**) will be reported to the coordinating study centre and there to the DSMB and the study steering committee (see below) to control safety issues and to discuss intervention or protocol amendments accordingly. An adverse event is any undesirable event that occurs whether or not considered to the participation in the study. Therefore, AEs can be any undesirable, unintentional, or unanticipated outcome or symptom or any disease in a timely relation to the study participation, independent of a suspected relation.

AE will be documented on designated CRF forms. A serious adverse event is defined as any event within the study timeframe fulfilling at least one of the following criteria:

- Death
- Live-threatening event
- Hospitalisation (required or prolonged)
- Event that results in disability
- Any event that an intervention to prevent one of the points above....

According to ICH-GCP guidelines, SAE(s) have to be reported within 24hours by email (gaps@ikem.cz, copy: jan.martinek@volny.cz). SAE have to be reported to the local ethics committee of the study site.

CRFs as well as all study related documents will be kept at least 10 years after study termination. Any study subject is allowed to withdraw her / his consent for study participation at any time for any given reason.

16. References

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Appendix 1:

Steering Committees (SC)
All lead investigators will be steering committee members. One lead investigator per country will be nominated as national coordinator

Data and Safety Monitoring Board (DSMB)
Organisation of steering committee meetings
Reporting SAEs (*Serious adverse events)*
Assistance with international review, board/independent ethics committee applications
Data verification
Randomisation, unblinded analysis of result

Data Manager
Maintenance of trial IT system:

a) Mgr. Jan Mareš (IKEM)
b) M.D. Martin Janicko Ph.D, 1 Department of Internal medicine, Pavol Jozef Safarik University in Kosice, Louis Pasteur University hospital, 04001 Kosice, Slovak Republic

Data entry and verification:

a) M.D. Rastislav Hustak, Gastroenterology Department, University Hospital of Trnava and FZsPTU, SlovakRepublic
b) M.D. Martin Janicko Ph.D

Appendix 2.
Questionnaires

GSCI score

		none	Very mild	Mild	Moderate	Severe	Very severe
1.	Nausea	0	1	2	3	4	5
2.	Retching	0	1	2	3	4	5
3.	Vomiting	0	1	2	3	4	5
4.	Stomach fullness	0	1	2	3	4	5
5.	Not able to finish a normal sized meal	0	1	2	3	4	5
6.	Feeling extensively full after meals	0	1	2	3	4	5
7.	Loss of appetite	0	1	2	3	4	5
8.	Bloating	0	1	2	3	4	5
9.	Stomach or belly visibly larger	0	1	2	3	4	5

1-3 = nausea/vomiting
4-7 = post-prandial fullness/early satiety
8-9 = bloating

Calculation:
Total GSCI score = arithmetic mean of the three symptom subscales
Subscores = arithmetic means of (1-3), (4-7) and (8-9)

PAGI-SYM score

	None	Very mild	Mild	Moderate	Severe	Very severe
1. Heartburn (burning pain rising in your chest or throat) during the day	0	1	2	3	4	5
2. Regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	0	1	2	3	4	5
3. Heartburn (burning pain rising in your chest or throat) when lying down	0	1	2	3	4	5
4. Regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	0	1	2	3	4	5
5. Feeling of discomfort inside your chest during the day	0	1	2	3	4	5
6. Bitter, acid or sour taste in your mouth	0	1	2	3	4	5
7. Feeling of discomfort inside your chest at night (during sleep time)	0	1	2	3	4	5
8. Vomiting	0	1	2	3	4	5
9. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
10. Retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
11. Stomach fullness	0	1	2	3	4	5
12. Not able to finish a normal-sized meal	0	1	2	3	4	5
13. Feeling excessively full after meals	0	1	2	3	4	5
14. Loss of appetite	0	1	2	3	4	5
15. Bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
16. Stomach or belly visibly larger	0	1	2	3	4	5
17. Upper abdominal (above the navel) discomfort	0	1	2	3	4	5
18. Upper abdominal (above the navel) pain	0	1	2	3	4	5
19. Lower abdominal (below the navel) pain	0	1	2	3	4	5
20. Lower abdominal (below navel) discomfort	0	1	2	3	4	5

1 - 7 = heartburn/regurgitation
8 - 10 = nausea/vomiting
11 - 14 = post-prandial fullness/early satiety
15 - 16 = bloating
17 - 18 = upper abdominal pain
19 - 20 = lower abdominal pain

Calculation:

Subscale scores are calculated by averaging across items comprising the subscale; scores vary from 0 (none or absent) to 5 (very severe). The half-scale rule is applied for missing data (i.e., the subscale score is calculated by using the mean of non-missing items; when more than 50% of items are missing, the score is set to missing).
A total score is calculated by averaging all subscale scores.

Appendix 3:

Egg Beaters Gastric Emptying Scintigraphy

Items needed for Egg Beaters Gastric Emptying Scintigraphy:
118 mL of liquid egg whites (Egg Beaters; egg substitute): 99% real eggs, cholesterol free, fat free, low calorie (120 g Egg Beater, 60 kcal, ***approx. two large eggs****), 2 slices of wheat bread (120 kcal), Strawberry jam (30 g, 74 kcal) Water (120 ml). Technetium-99m 0.75 mCi*

To prepare the meal, 0.75 Ci of 99Tc sulfur – colloid is mixed with liquid egg whites, the mixture is cooked in a microwave or on a hot nonstick skillet. The Egg Beater mixture is stirred once or twice during cooking and is cooked until it has the consistency of an omelet (3-5 min). The bread is toasted. Jelly is spread on the bread, and a sandwich is made of the jellied bread and cooked egg mixture. The subject completes the sandwich meal quickly, within max. 10 minutes.

Gastric emptying studies are generally performed in the morning. Patient should be fasting overnight or for at least 6 hours. Patients should generally stop prokinetic agents, and anticholinergic agents that can affect gastric emptying for 3 days prior to the test. should have a reasonable glucose level for the test. Generally, the fasting glucose in diabetic patients should be between 75 and 275 mg/dL (4.2 to 15.3 mmol/l). Diabetic patients should self-administer their insulin with meal ingestion, generally ½ what they take normally. The nutritional composition of the meal is 69-72% carbohydrate, 22-24% protein, 2% fat and 2% fiber. Other alternative meals may also be useful for patients with egg allergies or intolerance to eggs, and patients with gluten-sensitive enteropathy according local principles.

Gastric Emptying of Solids 13C-Octanoic Acid Breath Test (Leuven Model)

The test is performed after an overnight fast.

A dose of 100 mg (1-^{13}C)-Octanoic Acid is administered orally in a solid test meal. The test meal is standardized and consists of one scrambled egg with two slices of white bread and 5 g of margarine, together with 150 ml water (swallowed immediately after ingestion of the meal). The total caloric content is 250 kcal. The egg yolk is doped with 100 mg (1-^{13}C)-Octanoic Acid and fried separately from the egg white. The meal is consumed within 10 minutes.

Breath samples are collected before (2x), every 5 minutes during the first 30 minutes (0.5 h) and every 15 minutes for the next 210 minutes (3.5 h) after the ingestion of the (1-^{13}C)-Octanoic Acid. ^{13}C enrichment in breath CO_2 is determined by Isotope Ratio Mass Spectrometry (IRMS). The equation of the breath test results is obtained by 2 non-linear regression curves fitting the % dose ^{13}C recovered in breath per minute and the cumulative % dose recovered in breath. From this equation the half emptying time and the lag phase time are calculated as well as the gastric emptying coefficient (GEC).

Appendix 4

The PAGI-QOL (Quality of Life Questionnaire)

The following questions ask about how some of the gastrointestinal problems you may be experiencing (such as pain, discomfort or other problems) may have affected your overall quality of life and well-being in the past 2 weeks.
Please answer every question by *circling the number* that best represents your opinion. There are no right or wrong answers.

During the past 2 weeks, because of your gastrointestinal problems, how often…	*None of the time*	***A little of the time***	***Some of the time***	***A good bit of the time***	***Most of the time***	***All of the time***
1. have you had to depend on others to do your daily activities?	0	1	2	3	4	5
2. have you avoided performing your daily activities?	0	1	2	3	4	5
3. have you had difficulty concentrating?	0	1	2	3	4	5
4. has it taken you longer than usual to perform your daily activities?	0	1	2	3	4	5
5. have you felt tired?	0	1	2	3	4	5
6. have you lost the desire to participate in social activities such as visiting friends or relatives?	0	1	2	3	4	5
7. have you been worried about having stomach symptoms in public?	0	1	2	3	4	5
8. have you avoided performing physical activities or sports?	0	1	2	3	4	5
9. have you avoided traveling?	0	1	2	3	4	5
10. have you felt frustrated about not being able to do what you wanted to do?	0	1	2	3	4	5
11. have you felt constricted in the clothes you wear?	0	1	2	3	4	5
12. have you felt frustrated about not being able to dress as you wanted to?	0	1	2	3	4	5
13. have you felt concerned about what you can and cannot eat?	0	1	2	3	4	5
14. have you avoided certain types of foods?	0	1	2	3	4	5
15. have you restricted eating at restaurant or at someone's home?	0	1	2	3	4	5
16. have you felt less enjoyment in food than usual?	0	1	2	3	4	5
17. have you felt concerned that a change in your food habits could trigger your symptoms?	0	1	2	3	4	5
18. have you felt frustrated about not being able to choose the food you wanted to?	0	1	2	3	4	5
19. have you left frustrated about not being able to choose the type of beverage you wanted to?	0	1	2	3	4	5
20. has your relationship with your spouse or partner been disrupted?	0	1	2	3	4	5
21. has your relationship with your children or relatives been disrupted?	0	1	2	3	4	5
22. has your relationship with your friends been disrupted?	0	1	2	3	4	5
23. have you been in a bad mood?	0	1	2	3	4	5
24. have you felt depressed?	0	1	2	3	4	5
25. have you felt anxious?	0	1	2	3	4	5
26. have you felt angry?	0	1	2	3	4	5
27. have you felt irritable?	0	1	2	3	4	5
28. have you felt discouraged?	0	1	2	3	4	5
29. have you been stressed?	0	1	2	3	4	5
30. have you felt helpless?	0	1	2	3	4	5

The PAGI-QOL contains 30 items with five subscales:

(1) daily activities (1 – 10)
(2) clothing (11 – 12)
(3) diet/food habits (13 – 19)
(4) relationship (20 – 22)
(5) psychological well-being and distress (23 – 30)

The PAGI-QoL questionare contains of 30 items with five subscales: (1) daily activities; (2) clothing; (3) diet/food habits; (4) rela- tionship; and (5) psychological well-being and distress. Each items are scored on a 6-point Likert scale, with response options ranging from 0 (none) to 5 (severe problem all of the time). Subscale scores are calculated by averaging the item responses. A total score is calculated by averaging subscale scores.

Appendix 5
Perioperative protocol

The day before G-POEM (POD-1)

- Fasting for 24 to 48 hours (according the investigator)
- Current weight, QoL, ASA physical status
- Endoscopic examination with event. removal of the remaining food (optional)
- Anesteshiologist´s examination
- Blood sampling for: Haemoglobin, WBC, RBC, Thrombocytes, CRP, Quick, Haemoglobin A1c in patients with DM. Other blood tests possible. - – may also be done in the morning prior to the procedure ("day 0").
- Liquids up to 20:00 hours, then nil per os
- Supportive infusions according to an attending physician

Day „ 0 " (procedure)

- Omeprazole 40 mg iv (or similar PPI) will be given to patients at 6.00 – 7.00 o´clock and then 3xdaily until the morning on POD 1 (saline only will be given in the sham group). Please, keep patients and hospital staff blinded as much possible.
- 15 to 60 minutes before the procedure, the patients (active group) will be administered intravenous antibiotics: e.g. Ceftriaxone 2 gr (or similar antibiotics) and Metronidazole 500mg. Patients in the sham group will be given placebo (normal saline).
- After the procedure, nil per os for 24 hours (both group).
- Analgesics and anti-emetics as needed.

Day after G-POEM (POD1)

- Morning (6:00 am): last dose of i.v. omeprazole 40 mg in active arm (saline in placebo group), then esomeprazole 2x40 mg (or other PPI) for at least 3 weeks and then on demand for all patients.
- Ceftriaxone 2 gr i.v. (or similar antibiotic), placebo (normal saline) in the sham arm.
- Mucosal integrity will be confirmed with either endoscopy or X-ray with water soluble contrast or both at the discretion of an investigator. *If necessary, additional intervention to close mucosal incision will be used.*
- If no leak or other problems are detected, patients will be allowed to drink clear fluids and begin re-alimentation.
- Analgesics if necessary
- Blood sampling: blood count, coagulation, creatinine, ions, CRP, glycemia
- Discharge from a hospital according to the clinical condition

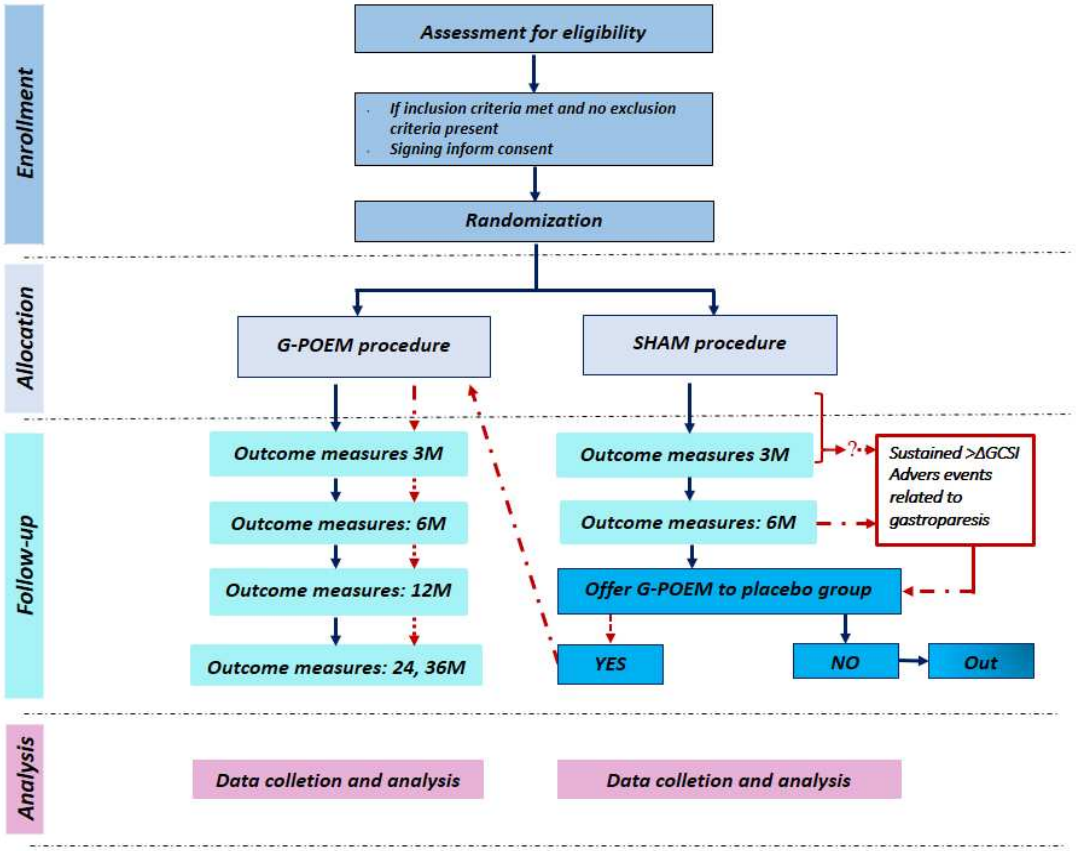
Second day after the procedure (POD2)

- PPI orally – all patients
- ATB only, if necessary

Recommendation: After patient´s discharge, it is advisable to keep patient´s allocation at the Clinic in a closed envelope. I case of need (e.g. urgent visit), the envelope can be opened and a physician on duty has an immediate access to the treatment´s allocation.

Appendix 6

Study design



Appendix 7

Center ID and Patient IDs

Center	Center ID	Patients code
1. Department of Hepatogastroenterology, IKEM, Prague, Czech Republic	***01***	*1 - 50*
2. University Medical Center Hamburg- Eppendorf, Germany	***02***	*1 – 50*
3. Translational Research in GastroIntestinal Disorders, Leuven, Belgium	***03***	*1 – 50*
4. King's Institute of Therapeutic Endoscopy, London, UK	***04***	*1 - 50*
5. III. Medizinische Klinik, Medical Center/Klinikum Augsburg, Germany	***05***	*1 – 50*
6. Department of Hepatogastroenterology at Cliniques universitaires St-Luc, Brussels, Belgium	***06***	*1 – 50*
7. Department of Surgical Gastroenterology, Karolinska University Hospital, Stockholm, Sweden	***07***	*1 – 50*
8. Department of Gastroenterology and Hepatology, Amsterdam, The Netherlands	***08***	*1 – 50*
9. Department of Internal Medicine, University Hospital Trnava, Slovak Republic	***09***	*1 – 50*
10. The Department of Surgical Gastroenterology L, Denmark	***10***	*1 – 50*
11. Jeesenius Faculty of Medicine in Martin, Clinic of Gastroenterological Internal Medicine, Slovak Republic	***11***	*1 - 50*
12. Center for Endoscopic and Therapeutics Research, The University of Chicago, USA	***12***	*1 - 50*
13. Regional Institute of Gastroenterlogy, Cluj-Napoca, Romania	***13***	*1 - 50*
14. Department 2nd Dept. of Internal Medicine – Gastroenterology, University Hospital in Hradec Kralove, Czech republic	*14*	*1 - 50*
15.		
16.		
17.		
18.		
19.		

1. **Codification (for CRF)**

Name : _____
Birth date: _____

Patient ID ☐☐ – ☐☐
Center ID ***Patient code***

Examples:

Name : XXX
Birth date: DD.MM.YY

0 1 – 0 1
Center ID ***Patient code***
(IKEM) *(Patient No 1)*

Name : XXX
Birth date: DD.MM.YY

0 2 – 1 1
Center ID ***Patient code***
(Hamburg) *(Patient No 11)*

Appendix 8:

Adverse event (AE) / Serious Adverse Event (SAE) Report Form

Definition: An adverse event is any undesirable, unintentional or unanticipated event that occurs during use of the investigational device, whether or not considered related to the therapy. A serious adverse event (SAE) is an event that is: fatal, life-threatening, results in persistent or significant disability/incapacity, requires or prolongs inpatient hospitalization. SAE must be reported within 24 hours to the Prague study center (gapc@ikem.cz, copy: jan.martinek@volny.cz) and the Ethics Committees/IRB if applicable.

Hospital visits due to follow up visits are not considered to be SAE.

□ Initial report

□ Consecutive report

Date AE start: _____ / _____ / _____ (DDMMYY)
□ expected event □ unexpected event

Event related to G-POEM / SHAM procedure
□ No □ Possibly □ Yes

Complication: □ Perforation □ Bleeding □ Infection □ Other

Please describe complication:
_____
_____

Intervention required: □ No □ Yes
please describe intervention:
_____
_____

medication required: □ No □ Yes

medication(s):
_____
_____
_____
_____

Report of a Serious Adverse Event

Hospitalization or prolongation of hospital stay required (SAE):
□ Yes □ No

If yes, please report within 24 hours to the Prague study center and Ethics Committee/IRB if applicable!

Date of hospitalisation/ - prolongation_____ (DDMMYY)

Date hospital discharge_____ (DDMMYY)

- -
- -

□ event resolved □ event ongoing

□ long term sequela □death □ unknown

Description/ comment: _____

Date AE stop: _____ / _____ / _____ (DDMMYY)

Data and Safety Monitoring Board

IKEM, Department of hepatogastroenterology

8th of February 2021, Prague

Study: A Randomized, Sham and Cross-Over-Controlled Trial of per-oral endoscopic pyloromyotomy (G-POEM) in patients with refractory gastroparesis (GREG)

ClinicalTrials.gov identifier: NCT03356067

Grant number: 17-28797A

To the principal investigator

Prof. Jan Martínek

Department of hepatogastroenterology

IKEM

Vídeňská 1958/9, Prague

The DSMB met at 29th of January 2021 and reviewed interim results after 41 subjects have been randomized and 33 patients completed the M6 visit. At present, there is a significant difference regarding the main endpoint (treatment success at 6 months) in favor of the active group (vs. sham). Also, 100 % of patients, who had undergone cross-over G-POEM after they underwent a sham procedure, experienced a treatment success. Based on these results, the Committee recommends to stop enrolment now because:

1. It would be highly unlikely that during the further course of the study, the results would change qualitatively. The p-value of the logistic regression analysis comparing the treatment success between G-POEM and sham groups is equal to p=0.003. Since no interim stopping scheme with pre-specified corrected alpha thresholds was specified, we primarily consider the Haybittle–Peto boundary. This boundary states the critical value of p=0.001 at all interim analyses and sometimes p=0.002 is used if only one interim analysis is performed. Our obtained p-value does not directly reach this level of significance, but taking into account the heuristic nature of the Haybittle–Peto approach and the fact that this approach is considered very conservative for stopping a trial, we believe that the evidence in favor of G-POEM efficacy is sufficient for stopping further enrollment.
2. Even if the strict statistical threshold for early trial termination is not met, ethical reasons should be considered. In particular, the risks related to general anesthesia in the sham procedure can not be further justified in the light of the current results. The Board consider it unethical to continue with study enrolment.

There should be further studies assessing the key question of how to select patients who will benefit from G-POEM, but we believe that there is no need for further inclusion of sham procedures.

Data and Safety Monitoring Committee members:

Chairperson:

MUDr. Alice Štrosová – gastroenterologist

Head physician

MEDIENDO s.r.o.

Thámova 13, 186 00 Praha 8-Karlín

MUDr. Jana Krajčíová – gastroenterologist

MUDr. Klára Chmelová – hepatologist

MUDr. Denisa Erhartová – gastroenterologist and hepatologist

MUDr. Martin Jerie – neurologist, independent specialist

Mgr. Barbora Bučková – statistician

MUC. Dagmar Dražilová – medical student

JUDr. Klára Daňková – lawyer

In Prague, 8th of February 2021

MUDr. Alice Štrosová

Head physician

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