PROTOCOL

Synopsis

A Study to Compare the Safety and Effectiveness of the 12-month Spatz3 Adjustable Balloon with the 6-Month Orbera Balloon in the Weight Management of Subjects

Study Design

1.1. Study Hypothesis

Confirmation that the 12-month Spatz3 Adjustable balloon is more effective than the 6-month Orbera balloon with 6-month dietican follow-up.

1.2. Primary Endpoint

Efficacy

1.2.1. The primary endpoint is the percent change in total body weight (%TBL) at 12 months.

1.2.2. Safety

The incidence, frequency, and severity of adverse events related to treatment with the device will be reported.

1.3. Design

The purpose of this study is to compare and confirm the superiority of a 12-month adjustable balloon over a 6-month non-adjustable balloon with 6-month dietician follow-up. The endpoint is %TBL at 12 months.

Subjects will be studied in a randomized open label single center study that will run 52 weeks. Subjects will be randomized to two treatment groups: Group 1- Spatz3 adjustable balloon 12-month implantation; and Group 2 – Orbera 6-month implantation with additional 6 months of dietician follow-up after balloon extraction. Fourty four eligible subjects will be randomized to treatment groups 1 and 2 and will undergo endoscopy and implantation of either the Spatz3 Adjustable Balloon or the Orbera Balloon, resulting in approximately 22 subjects in each group. All subjects will follow a calorie restricted diet designed by the dietician. The initial diet will be liquid and will be advanced as per the dietician's recommendations. Changes in diet will depend on subject tolerance to the balloon and specific food intolerances and will be adjusted frequently

by the dietician. The initial balloon volume will be 500 ml of 0.9% normal saline with 2 ml of a 1% solution of methylene blue. An adjustment will be performed for treatment Group 1 at Week 24 (±6 weeks) with the addition of 200-300 ml of 0.9% normal saline, as per section 1.6.2.1.3.3. The balloon adjustment procedure is done with an endoscopy procedure under the same sedation as the implantation procedure. The subjects will have follow up by the PI/Nurse Practitioner and the Dietician/Nutritionist periodically as per section 1.7.3. until extraction at 52 weeks. The Orbera treatment group will undergo balloon extraction at 6 months followed by monthly dietician vists for an additional 6 months. The study will terminate at the end of 12 months.

The Spatz3 Adjustable balloon System has been implanted for 12 months since 2012, with over 65,000 implantations in over 50 countries. It has been under the scrutiny of the regulatory authorities in all of these counties, and has an excellent safety record. To date, there has never been an adverse event or complaint after balloon extraction. During the 6 month follow up after balloon extraction in the Spatz3 FDA trial, not even one adverse event was reported during that period. Therefore, a follow up period after Spatz balloon extraction is not planned for this study.

1.4. Study Setting

The study will be conducted at the Asclepiades – Interna a Gastroenterologie, s.r.o. Medical Center. The maximum enrollment will be limited to 44 subjects.

1.5. Subjects

Participants will be patients between ages 18 years and 65 years inclusive, with a BMI ≥ 27 that meet the eligibility criteria below. All eligibility criteria must be met at the time of enrollment.

Inclusion criteria:

- Have a BMI ≥ 27;
- Be male or female, between 18 and 65 years of age, inclusive;
- Have a history of excess weight (BMI ≥ 27 kg/m^2) for at least 2 years and have failed more conservative weight-reduction alternatives, such as supervised diet, exercise and behavioral modification programs;
- Be willing to commit to a long-term low calorie (1000-1500 calories/day) supervised diet;

- Have reasonable weight loss expectations (accept a goal of losing up to 15% of body weight after 52 weeks);
- Be able to follow requirements outlined in the protocol, including complying with the visit schedule and behavioral modification program, and willing to undergo protocol-specific procedures, e.g., endoscopy, local sedation, general anesthesia, upper gastrointestinal radiography (UGI), electrocardiography (EKG), gastric motility testing, and/or clinical laboratory testing, and must be willing to take prescribed proton pump inhibitors (PPIs);
- Be able to provide written informed consent;
- Have successful completion of the pre-placement screening and educational programs supporting that the subject is an appropriate study candidate;
- Be willing to use contraception (e.g., birth control pills, condoms, abstinence) and avoid pregnancy during the study if female of child-bearing potential.

Exclusion criteria:

- Previous history of esophageal, gastric or duodenal surgery, any bariatric surgery, any hiatal hernia surgery, bowel obstruction surgery, adhesive peritonitis, and/or hiatal hernia $\geq$ 4 cm;
- A history of myocardial infarction in the previous 6 months: New York Heart Associate (NYHA) Class III or IV (heart failure) or cardiac arrhythmia (e.g. atrial fibrillation);
- History or symptoms of varices, bowel obstruction, congenital or acquired GI anomalies (e.g., atresias, stenosis, stricture, and/or diverticula), severe renal, hepatic, and/or pulmonary disease;
- History or symptoms of inflammatory bowel disease, such as Crohn's disease;
- History of unstable thyroid disease;
- History of uncontrolled gastro-esophageal reflux;

- Type I diabetes;
- History of dysphagia, esophageal stricture or esophageal food impaction;
- Poor general health, in the opinion of the Placing and/or Evaluating Investigator, or presence of a specific medical condition that would increase the risks associated with endoscopy and/or placement of the Spatz3;
- Symptomatic congestive heart failure, cardiac arrhythmia or unstable coronary artery disease.
- Pre-existing respiratory disease such as chronic obstructive pulmonary disease (COPD);
- Specific diagnosed genetic or hormonal cause for obesity such as Prader Willi syndrome
- History or symptoms of esophageal or GI motility disorders (e.g., gastroparesis, achalasia, diffuse esophageal spasm) or symptoms of esophageal stricture;
- Ongoing treatment with anticoagulants, steroids, aspirin > 100 mg, non-steroidal anti-inflammatory drugs (NSAIDS), or other medications known to be gastric irritants, and inability or unwillingness to discontinue the use of these concomitant medications;
- Evidence of untreated psychiatric or eating disorders, such as major depression, schizophrenia, substance abuse;
- Pregnancy, breast-feeding, or intention of becoming pregnant during the study (if female of childbearing potential);
- A condition, or is in a situation, which in the Evaluating and/or Placing Investigator's opinion may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.

1.6. Informed Consent

Prior to being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them. The written informed consent document is provided in ***Appendix A*** of this protocol. Subjects are free to withdraw consent at any time, irrespective of their initial consent.

After reading the informed consent document, the participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are

performed. A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

The investigator will not perform any exams or testing specifically required only for the clinical study until valid consent has been obtained.

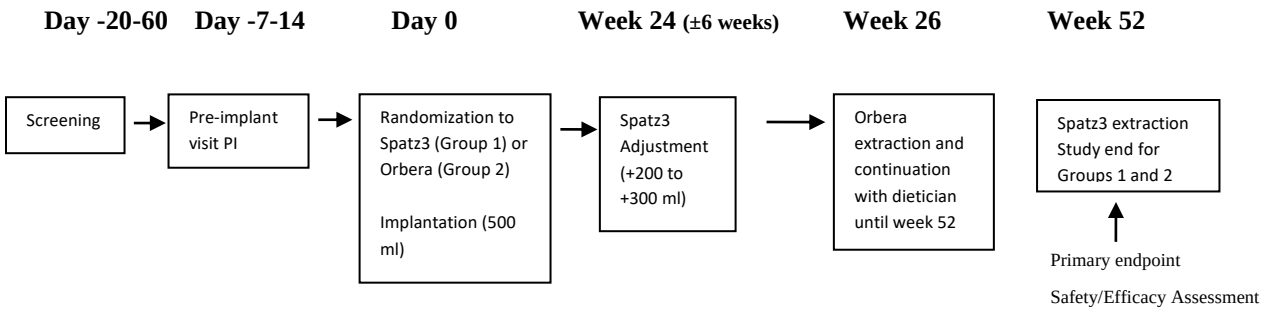
Any use of the device without obtaining informed consent shall be promptly reported (no later than 10 working days) to the Ethics committee.

1.7. Study Timeline

The study timeline is summarized in

Figure 1:

Figure 1: Study Timeline



1.7.1. Screening and Eligibility Assessment

Screening will be conducted by the investigator and documented on the PI Intake form (***CRF1 PI Intake***) and Screening Labs form (***CRF2 Screening Labs***). Screening must occur no more than 60 days prior to implantation.

Screening will include the following:

1. Screening exam by investigator (***CRF1 PI Intake***). Includes Medical history, Current medications, Body Weight and Height, Physical exam, Evaluation of inclusion/exclusion criteria.
2. Sign Informed Consent Form (***Appendix A: Informed Consent***)
3. Dietician intake - Baseline body weight, height, ideal body weight, excess weight, BMI, (***CRF4 Dietician Intake***)

4. Laboratory tests (± EKG, CXR)

*Laboratory Tests (***CRF2 Screening Labs)** include:

CBC: Hgb, Hct, WBC, Platelets

Chemistry panel: sodium, potassium, BUN, creatinine, glucose, SGOT(AST), SGPT(ALT), alkaline phosphatase, total cholesterol, TSH

$HgbA_{1C}$ (if diabetic)

EKG for subjects above the age of 40

CXR for subjects above the age of 60

The PI will review the results and determine eligibility of the subject. All potential subjects who pass the initial screening assessment must return for an additional visit within 14 days of the scheduled implantation procedure for the Pre-Implantation visit (***CRF3 Pre implant***). This will include an assessment of the following:

- Urine pregnancy test (women of child-bearing potential)
- Medications List

Subjects with a positive pregnancy test or who are taking medications listed in the exclusion criteria will be excluded from the study at this time, and will be considered to be screening failures.

1.7.2. Trial Intervention

1.7.2.1. Implantation

The Spatz3 and Orbera balloons are implanted in an outpatient setting via upper endoscopy under conscious sedation. The subject fasts from midnight the night prior to the procedure. Conscious sedation will utilize any combination of the following drugs at the discretion of the anesthesiologist -Propofol, Midazolam, Ketamine, Optalgin and a narcotic such as Fentanyl. A standard upper endoscopy is performed to rule out contraindicating findings such as a large hiatal hernia >4 cm), esophagitis that is Grade B, C or D, erosive gastritis or ulceration of the stomach or duodenum.

Prior to implantation of the Spatz3 Adjustable balloon, the balloon is prepared as follows: the Valve-Hold is inserted into the white catheter and the valve is connected to the extension tube, after which the Spatz balloon is secured to the endoscope by the insertion facilitator. The scope with balloon secured to its side is passed into the throat and continues into the esophagus and stomach. Upon arrival in the stomach a retroflex maneuver confirms the presence of the balloon in the stomach and below the gastro-esophageal junction. The scope is then straightened and the balloon is inflated by connecting the extension tube to the provided 60 ml syringe and a 500 ml

bag of Normal Saline. The 500 ml bag of Normal Saline will be injected with 2 cc of 1% Methylene Blue.

After final balloon volume is achieved, the extension tube is pulled until the valve exits the mouth, after which the extension tube is disconnected and replaced with the cap. The cap is allowed to enter the throat and passes on its own down the esophagus, followed by the endoscope which pushes it into the stomach, after which the scope is removed.

The adjustments will be performed at Week 24 (±6 weeks). The balloon will be extracted at week 52.

The Orbera balloon is inserted by passing it through the pharynx and into the esophagus and stomach. The balloon position is verified by the endoscopist and inflation ensues utilizing a 60 ml syringe and a 500 ml bag of Normal Saline. The 500 ml bag of Normal Saline will be injected with 2 cc of 1% Methylene Blue.

The Orbera balloon will be extracted at 26 weeks using extraction needle and extraction forceps.

1.7.2.1.1. Diet and Exercise

The subjects will be provided with dietary counseling throughout the study. The first dietician visit will commence less than 60 days prior to the implantation procedure. A diet plan will be reviewed with each subject and will be adjusted according to the needs of each subject (Appendix C: Diet Plan). In addition, exercise counseling will be given by the dietician with specific exercises detailed (Appendix D: Physical Exercise Program). The progressive exercise plan will have 3 phases that are gradually phased in over time.

1.7.2.1.2. Medications

All treatment arm subjects will receive the following oral medications for the implantation and upward adjustment procedures:

- Aprepitant (Emend) [implantation procedure only]125 mg immediately prior to or 1 hour after the procedure, 80 mg the morning after the procedure and another 80 mg two mornings after the procedure.
- Ondansetron 8 mg will be taken every 6 hours starting 1 hour after the procedure for 12 tablets (3-4 days);
- Anti-spasmodics (such as Spasmalgin 1-2 tablets up to 3 times a day (maximum 6 tablets/ 24 hours) or Hyoscyamine 0.125 mg 1-2 tablets sublingual up to 4 times daily or Buscopan 1-2 tablets up to 3 times daily) will be used on a prn basis
- A PPI (proton pump inhibitor such as Nexium, or Omepradex 20 mg, or Prevacid or Lanton 30 mg or Protonix 40 mg or equivalent PPI) will be taken daily for the entire period that the balloon is implanted and 1 week prior to the implantation to reduce acid in the stomach. This helps preserve the silicone and also controls acid reflux symptoms, should they arise.

- Probiotic, Acidophilus, 8-10 Billion CFU will be taken once daily for the entire period that the balloon is implanted.

During the implantation period, different symptoms may arise such as constipation, nausea, vomiting, bloating, abdominal pressure, heartburn, and diarrhea. These can be treated as discussed below.

Constipation is expected in the first week after implantation. It generally resolves after oral intake increases in the first 2 weeks. If it persists, standard treatments such as a teaspoon of mineral oil daily, Miralax or Normalax (OTC med) 17 gram+ 8 oz water twice daily or Laxadin 1-2 tablets twice daily (or equivalent laxative).

Nausea and/or vomiting or bloating or abdominal pressure can be treated with metoclopramide or Motilium (domperidone) – 10 mg orally up to 4 times in 24 hours.

Heartburn can be treated by increasing the PPI medication to twice daily; addition of metoclopramide or Motilium (domperidone) – 10 mg orally up to 4 times in 24 hours; addition of antacids such as Maalox, Mylanta, Gaviscon – 30 ml or 2 tablets every 3-4 hours (or 5 cc every 30 min) at the discretion of the PI.

Episodes of diarrhea can be expected in about 20% of patients periodically and is a sign of dietary non-compliance caused by food accumulation in the stomach and is due to a mild case of bacterial overgrowth in the stomach and small intestine. Should diarrhea develop, the subject will be instructed to revert to a full liquid diet, probiotic Acidophilus will be increased to 4 pills daily for 4 days and during those 4 days the PPI will not be taken. In the event those measures do not alleviate the diarrhea, treatment with Metronidazole 500 mg 3 times daily for 5 days will commence - generally the diarrhea improves on the first day of treatment. Some subjects have recurrence and require repeat treatment.

Foul-smelling belches may occur in 30-40% of subjects as a result of continuous administration of daily PPI medications in combination with balloon induced delayed gastric emptying. At the discretion of the investigator, these subjects may benefit from a 3-day holiday from the daily dose of PPI and the addition of Pepto Bismol or Kal Beten for 3-4 days. Gastro-esophageal reflux symptoms can be managed by use of antacids at a dose of 30 ml PO QID prn during the 3-day holiday.

For subjects intolerant to PPI medications (headache, diarrhea, abdominal pain, nausea, vomiting), the investigator will have the option of discontinuing the PPI and substituting any H2 Blocker medication at a twice daily dosing (Ranitidine 150 PO BID; Famotidine 20 mg PO BID or equivalent H2 blocker).

For Spatz3 subjects with spontaneous hyperinflation of the balloon the following protocol will be performed:

- Endoscopic deflation of the balloon completely
- Re-inflation with previous volume + 100 ml additional
    - Add 200 mg Cipro and 10 ml of Nystatin

- No Methylene Blue will be added

For Orbera subjects with spontaneous hyperinflation of the balloon, the balloon will be extracted, and the subject will be dismissed from the study.

1.7.2.1.3. Adjustments

1.7.2.1.3.1. Adjustments for Intolerance

The PI may make an adjustment to the balloon volume at any time if the patient has symptoms of continued nausea, vomiting, uncontrolled GE reflux or abdominal pain in spite of conservative symptomatic treatment.

For intolerance that continues more than 7-10 days beyond the first 5 days after implantation or that occurs at any time thereafter, the investigator should:

- remove 100 ml from balloon (when balloon volume is 400 ml), or
- remove 150 ml from balloon (when balloon volume is 450 ml or 500 ml)

The final volume should not be reduced below 300ml. If medications and balloon volume down adjustment do not alleviate the intolerance, the balloon should be extracted.

1.7.2.1.3.2. Unscheduled endoscopy

An unscheduled endoscopy may be performed at any time at the discretion of the investigator.

The following procedures will be applied to subjects who present with endoscopic findings based on an unscheduled endoscopy.

<u>Gastric Ulceration</u>

Subjects who present with an endoscopically confirmed gastric ulcer will be treated as follows and will have follow up endoscopy at the discretion of the investigator:

- **Ulcers whose smallest dimension (S) is ≥ 2cm, or if there are any stigmata of increased risk of bleeding, such as visible vessels or clots**

  The balloon should be extracted. Biopsy for H.pylori will be performed and treatment prescribed if positive.

  These subjects should be treated with the following regimen: with PPI medication twice daily for 3 months.

- **Ulcers whose smallest dimension (S) is ≥ 1 cm and < 2 cm**

  The Spatz balloon volume should be decreased by 150 ml (or 100 ml if starting volume is 400 ml) and subjects should be treated with the following regimen: increasing PPI

medication to twice daily for 2 months. A biopsy for H.pylori will be taken and treatment prescribed if positive.

These subjects will not undergo adjustment at week 24 (±6 weeks).

Orbera balloon subjects will have their balloon extracted and will be treated with the following regimen: increasing PPI medication to twice daily for 2 months. A biopsy for H.pylori will be taken and treatment prescribed if positive.

- **Ulcers whose largest dimension is ≥ 1 cm and whose smallest dimension (S) is < 1 cm.**

  The balloon volume should be decreased by 150 ml if the balloon volume is 450 ml or more (or 100 ml if balloon volume is 400 ml) and subjects should be treated with the following regimen increasing PPI medication to twice daily for 3 months. A biopsy for H.pylori will be taken and treatment prescribed if positive.

  These subjects will not undergo up adjustment at Week 24 (±6 weeks).

  Orbera balloon subjects will have their balloon extracted and will be treated with the following regimen: increasing PPI medication to twice daily for 2 months. A biopsy for H.pylori will be taken and treatment prescribed if positive.

- **Small Ulcers and Erosive gastritis**
  Spatz balloon subjects with ulcers < 1 cm in diameter in all dimensions (< 0.5 cm is not considered an ulcer) and erosive gastritis should be treated with the following regimen: increasing PPI medication to twice daily for 3 months. A biopsy for H.pylori will be taken and treatment prescribed if positive. Balloon volume reduction at the discretion of the PI.

  These subjects will not undergo up adjustment at Week 24 (±6 weeks).

  Orbera balloon subjects will be treated with the following regimen: increasing PPI medication to twice daily for 3 months. A biopsy for H.pylori will be taken and treatment prescribed if positive. Balloon extraction at the discretion of the PI.

<u>Non-Erosive Gastritis</u>

If non-erosive gastritis is found at endoscopy, subjects will be treated with increasing PPI medication to twice daily for 2 months. A biopsy for H.pylori will be performed and treatment prescribed if positive.

Esophagitis

Subjects who present with esophagitis will be treated as follows:

- For subjects with esophagitis grade C or D at endoscopy, the balloon will be extracted, with the following medication regimen given:
    - Increase PPI to BID
    - Add Metochlopramide or Domperidone 10 mg ac and Qhs
    - Add Gaviscon or Maalox 30 ml Q4h prn or Sucralfate suspension 1000 mg PO QID

- For subjects with esophagitis grade A or B at endoscopy, the balloon may be left in place, with the following medication regimen given for 2-3 months:
    - Increase PPI to BID
    - Add Metochlopramide or Domperidone 10 mg ac and Qhs
    - Add Gaviscon or Maalox 30 ml Q4h prn or Sucralfate suspension 1000 mg PO QID

  These subjects will not undergo up adjustment at Week 24 (±6 weeks).

1.7.2.1.3.3. Adjustment at Week 24 (±6 weeks)

At week 24±6 weeks, all Spatz subjects will be evaluated to determine if an upward adjustment is clinically appropriate. The addition of 200-300 ml at the adjustment will be used based on the following algorithm:

1. Subjects who have recurring abdominal pain, nausea, vomiting or acid reflux will not receive a balloon volume up adjustments.
2. Subjects who have reached goal weight will not receive a balloon volume up adjustment.
3. Subjects who underwent a prior unscheduled endoscopy with findings of a gastric ulcer, or any grade esophagitis will not receive an adjustment.
4. For all other subjects, endoscopy will be performed, and adjustments/treatment decisions will reflect the following algorithm:
    a. For subjects with gastric ulceration or any grade esophagitis found at the adjustment endoscopy, **no upward adjustment** will be performed.

b. Redness in the esophagus or stomach without significant erosion is not a contraindication to up adjustment.
c. For the week 24 (±6 weeks) week adjustment, an additional 200-300 ml of 0.9% Saline will be added to the balloon at the discretion of the PI.
    - 200 ml will be added for those subjects with mild GI symptoms or mild signs such as burps, bloating and gassiness
    - 250 ml will be added for those without any GI symptoms, but with mild signs such as burps, bloating and gassiness
    - 300 ml will be added for those without any GI symptoms or signs (burps, gassiness, bloating)

Subjects who present with an endoscopically confirmed gastric ulcer will be treated as detailed in section 1.7.2.1.3.2.

1.7.2.1.4. Procedures

1.7.2.1.4.1. Adjustment procedure

The balloon adjustment procedure is done with an endoscopy procedure under the same sedation as the implantation procedure.

The adjustment procedure requires the patient to be on the following dietary restrictions:

- 72 hours prior to the procedure: Soft food only, no meat or vegetables in any form.
- 48 hours prior to the procedure: Full liquids only.
- 24 hours prior to the procedure: Clear liquids only.
- 12 hours prior to the procedure: No food or liquids by mouth.

The adjustment procedure is performed under conscious sedation by the anesthetist similar to the implantation procedure. The endoscope is introduced in the usual manner and the suture loop on the valve cap is located. The loop is grasped and the valve is pulled out of the mouth and attached to the extension tube, after which it is released to the back of the throat. The adjustment commences by utilizing the extension tube 3-way stopcock. Following completion of the adjustment, the extension tube is pulled until the valve exits the mouth and the extension tube is removed and exchanged with the cap. The cap is allowed to enter the throat and passes on its own down the esophagus, followed by the endoscope which pushes it into the stomach, after which the scope is removed.

1.7.2.1.4.2. Extraction Procedure

The extraction procedure requires the patient to be on the following dietary restrictions:

- 72 hours prior to the procedure: Soft food only, no meat or vegetables in any form.

- 48 hours prior to the procedure: Full liquids only.
- 24 hours prior to the procedure: Clear liquids only.
- 12 hours prior to the procedure: No food or liquids by mouth.

The extraction procedure is performed under conscious sedation by the anesthetist similar to the implantation procedure.

For Spatz subjects, the endoscope is introduced in the usual manner and the suture loop on the balloon is located. The loop is grasped and the valve is pulled out of the mouth and attached to the extension tube, after which it is released to the back of the throat. The 3 way stopcock on the extension tube is connected to the suction machine to drain the balloon (or it can be done via syringe by hand. Following complete drainage of the balloon, the endoscope is introduced and confirms complete drainage of the balloon. The extension tube is pulled until the valve exits the mouth and the inflation catheter is pulled gently until the balloon exits the mouth. An alternative method for extraction utilizes the standard balloon needle catheter to drain the balloon followed by extraction using a balloon grasping forceps. The scope is then reinserted to inspect for any mucosal damage.

For Orbera subjects, the balloon is punctured with a gastric balloon needle and drained completely. The balloon is then extracted sing a grasping forceps or snare. The scope is then reinserted to inspect for any mucosal damage.

Assessment / Procedure	**Screening Assessments (< 60 days prior to implant)**	**Within 14 Days Prior to implant**	**Implant**	**PI/NP/RN and Dietitian/Nutritionist** **Spatz: Follow-Up3* Assessment at 2 weeks(± 3 days), 7 weeks(± 7 days), 10 weeks(± 7 days), 18 weeks(± 2 weeks), 25 weeks(± 2 weeks), 35 weeks(± 2 weeks), 45 weeks(± 2 weeks).** **Orbera:** **Follow-Up3* Assessment at 2 weeks(± 3 days), 7 weeks(± 7 days), 10 weeks(± 7 days), 18 weeks(± 2 weeks), 25 weeks**	**Dietitian/Nutritionist Follow-Up[3]* Assessment weeks** **Visits at 1 week(± 3 days), 2 weeks(± 3 days), 4 weeks(± 7 days), 7 weeks(± 7 days), 10 weeks(± 7 days), 15 weeks(± 2 weeks), 20 weeks(± 2 weeks), 25 weeks(± 2 weeks), 30 weeks(± 2 weeks), 35 weeks(± 2 weeks), 40 weeks(± 2 weeks), 45 weeks(± 2 weeks), 50 weeks(± 2 weeks).**	**Adjustment (Spatz)** **Week 24(±6 weeks)**	**Extraction** **Orbera: Week 26** **Spatz: Week 52**	
Informed Consent	X							
Date of birth/gender	X							
Body Weight	X	X	X	X		X	X	
Body Height	X							
BMI	X	X	X					
Ideal weight/ Excess Weight	X							
Medical History	X							
Physical Exam[1]	X			X		X		
CBC[2] Chemistry Panel[2]	X							
HgbA1C2 IF DIABETIC	X							
EKG*(Females and Males >40 y/o)	X							
CXR (Females and Males >60 y/o)	X							
Inclusion and Exclusion Criteria	X							
Develop/Review Dietary Plan	X							
Dietary follow up Assessment				X				
Investigator or Nurse follow up				X				

[1] Investigator or co-investigator must perform physical exam.
[2] See section 1.7.1 for required tests
[3*] PI/RN and Dietician follow-up can be done via telephone in 50% of visits from week 10 and onward

Medications List (PI/RN)	X	X		X				
Urine Pregnancy Test women of child bearing potential*	X	X						
Adverse Events/Device Complications			X	X		X		
Verify Birth Control for Females	X							

1.7.2.1.5. Device Failures

If a balloon deflation or other device failure due to device malfunction or operator error occurs during the implantation or adjustment procedures or follow-up period, the investigator will replace the failed device with a new device unless doing so is not in the best interest of the patient. All device failures will be reported to the sponsor. The number of device failures and the circumstances under which they occurred will be included in the final Study Report.

1.7.3. Follow-Up Schedule

Follow-up visits for patients will occur according to the following schedule:

- PI or Nurse:
    - Spatz: Visits at 2 weeks(± 3 days), 7 weeks(± 7 days), 10 weeks(± 7 days), 18 weeks(± 2 weeks), 25 weeks(± 2 weeks), 35 weeks(± 2 weeks), 45 weeks(± 2 weeks).
    - Orbera: Visits at 2 weeks(± 3 days), 7 weeks(± 7 days), 10 weeks(± 7 days), 18 weeks(± 2 weeks), 25 weeks(± 2 weeks),
- Dietician/Nutritionist:
    - Spatz and Orbera: Visits at 1 week(± 3 days), 2 weeks(± 3 days), 4 weeks(± 7 days), 7 weeks(± 7 days), 10 weeks(± 7 days), 15 weeks(± 2 weeks), 20 weeks(± 2 weeks), 25 weeks(± 2 weeks), 30 weeks(± 2 weeks), 35 weeks(± 2 weeks), 40 weeks(± 2 weeks), 45 weeks(± 2 weeks), 50 weeks(± 2 weeks).
- ***Note: 50% of follow-up visits with Dietician/Nutritionist and PI from week 10 and onward may be done via telephone and documented on CRF.***

Each follow-up visit will include:

1. Clinical assessment by PI or nurse practitioner or RN (***CRF5 PI Follow Up***)
2. Dietary Assessment - (***CRF6 Dietician Follow Up***)

3. Record adverse events, device complications (***CRF7 AEs, Complications***)
4. Weight to be done by blinded personnel. In order to minimize bias, an uninvolved third party will measure all weights and record those weights in Appendix E with his/her signature. (***Appendix E:*** Blinded Weights)

1.8. Participant Retention

All patients will be encouraged to complete study follow-up, and all reasonable efforts will be made to ensure completeness of follow-up

It is understood that study participants may withdraw consent for study participation at any time irrespective of their reasons. The investigators may also withdraw a recipient from the study in order to protect their safety and/or if they are unwilling or unable to comply with the required study procedures.

In the event of a patient withdrawing from the trial, the reason for withdrawal must be documented on the CRF.

1.9. Definition of the End of the Trial

The trial will end after completion of the week 52 (± 7 days) visit for the last subject enrolled in the trial and a final study report will be generated. The Spatz3 Adjustable balloon System has been implanted for 12 months since 2012, with over 65,000 implantations in over 50 countries. It has been under the scrutiny of the regulatory authorities in all of these counties, and has an excellent safety record. To date, there has never been an adverse event or complaint after balloon extraction. During the 6 month follow up after balloon extraction in the Spatz3 FDA trial, not even one adverse event was reported during that period. Therefore, a follow up period after extraction for Spatz subjects is not planned for this study.

2. DEVICES

2.1. Spatz3 and Orbera

2.1.1. Spatz3 Device Description

The Spatz3 device consists of a balloon positioned around a curved catheter inside the balloon, and whose catheter continues and exits outside of the balloon. The external catheter houses the stretchable inflation tubing.

Figure 2: Spatz3 Prior to Implant

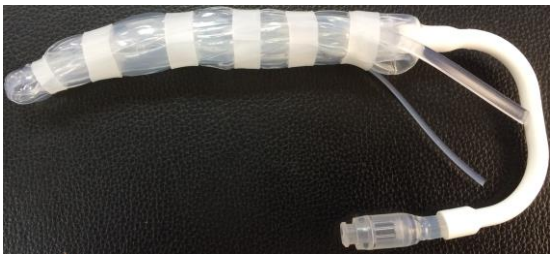
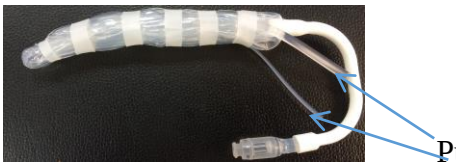


Figure 3: Spatz3 during Implantation

The Spatz3 balloon is wrapped by 6 silicone bands during shelf life, which gives it a tapered profile. The bands are removed using the "band-off" silicone pull strings prior to implantation.

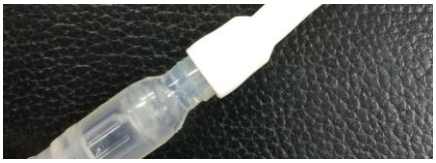


Pull both silicone strings to the left to remove all bands

The valve is secured to the white catheter with "valve-hold."


Valve Hold


Pushing Valve Hold into White catheter

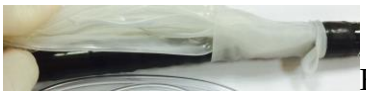

Valve Hold inside white catheter

The balloon is secured to the scope with the insertion facilitator.


Insertion Facilitator (as supplied)


Dressed on distal tip of scope w/ balloon ready to be secured


Rolled over balloon (2 holes to be used to secure to scope)


Balloon secured and insertion facilitator secured to scope

The balloon is inflated, adjusted and deflated via connection to an extension tube which has a 3-way stopcock at its proximal end. The extension tube is connected to the valve for all procedures and is provided in the packaging along with a 60 ml syringe (section 4.3.3.2 for details of all procedures).

The stretchable inflation tube design of the Spatz3 device permits balloon volume adjustment at the time of placement, and at a later time. Initial balloon volumes range from 400 cc to 550 ml. The minimum and maximum balloon volumes will range from 300 ml (an initial balloon volume of 400 or 450 ml that has been adjusted down to 300 ml due to intolerance) to 900 ml (an initial balloon volume of 550 ml that has been adjusted upward to 900 ml due to lack of any balloon effect in the first 2 weeks after implantation).

Figure 4: Inflation tube at rest

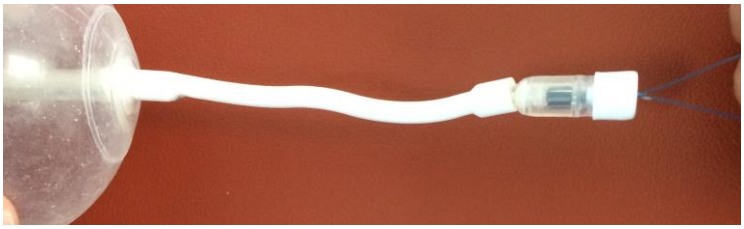
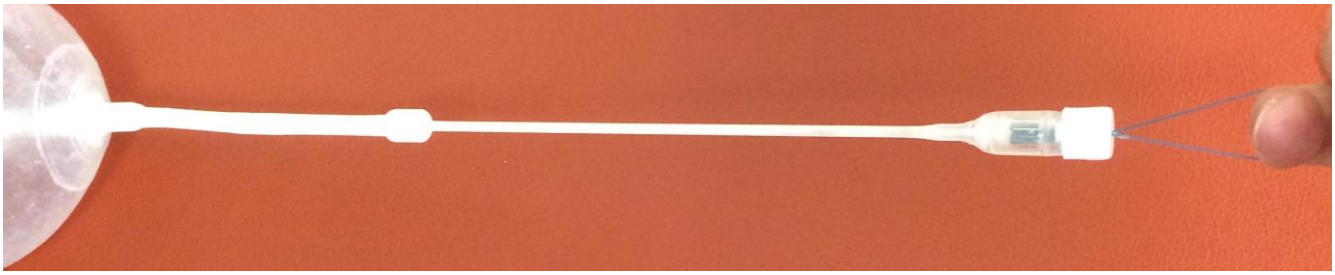


Figure 5: Inflation Tube partially stretched



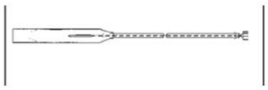
A retractable/stretchable silicone inflation tube allows the balloon to have its volume adjusted after initial insertion, while the balloon remains in the stomach (Figure 4 and Figure 5). The inflation tube is a 10cm long stretchable soft silicone tubing with an inner diameter of 2mm and an outer diameter of 4mm. The stretchable inflation tube is attached to the distal end of the catheter that resides within the balloon and exits the catheter just behind the balloon and is accessible for future adjustments. The inflation tube travels within the soft catheter outside of the balloon and exits where it is attached to a luer-lock valve. The valve is closed with a cap. The valve has within it a silicone piece that prevents fluid escape even when the cap is off. The

balloon is filled with saline and methylene blue (in the event of a balloon deflation the urine turns blue).

2.1.2. Orbera Device Description

ORBERA™ is placed in the stomach and filled with saline, causing it to expand into a spherical shape (Figure 2). The filled balloon is designed to occupy space and move freely within the stomach. The expandable design of ORBERA™ permits a fill volume range of 400cc (minimum) to a maximum of 700cc (refer to section 11.2 for filling guidelines). Once filled, the ORBERA™ volume is not adjustable. A self-sealing valve permits detachment from external catheters

The ORBERA™ balloon is positioned within the Placement Catheter Assembly. The Placement Catheter Assembly (Figure 3) consists of a 6.5mm external-diameter silicone catheter, one end of which is connected to a sheath in which the collapsed balloon resides. The opposite end is connected to a Luer lock connector for attachment to a filling system. Length markers are provided as a reference on the fill tube.



A guidewire has been inserted into the silicone placement catheter for increased rigidity during placement. A filling system consisting of an IV spike, fill tube and filling valve is provided to assist in the balloon deployment.

2.1.3. Additional Components and Adjunct Devices

The following additional items are not supplied by Spatz FGIA, but are used during the implantation, adjustment, and extraction procedures.

Sterile Saline Solution

Sterile saline solution is used to fill the balloon to the desired volume.

Methylene Blue

USP 1% methylene blue (Akorn 1% Methylene Blue Injection, NDC 17478-504-01) is added to the saline to provide a visual indicator to the patient (i.e., blue-green urine) when saline solution is released from a deflated balloon.

Endoscopic Rat Tooth Grasping Forceps

Rat tooth grasping forceps are recommended for use during the balloon adjustment and removal procedures to grab the suture loop at the top of the cap.

Large Polypectomy Snare

A large polypectomy snare may be used during the balloon removal procedure to grab the valve.

Needle Extraction Catheter

A specific needle extraction catheter used to puncture balloon and drain balloon.

Extraction Grasping Forceps

Used to grasp deflated balloon and extract it**.**

2.2. Device Labeling

All components of the Spatz3 and the Orbera device will be labeled with the CE approved Spatz3 label that is used for commercial use.

2.3. Adverse Events

2.3.1. Definitions

The following definitions will be used:

Adverse Event

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) whether or not related to the study intervention.

Serious Adverse Event (SAE)

An adverse event that meets one of the following criteria

- Led to death
- Resulted in serious deterioration in the health of the subject that results in:
- Life-threatening illness or injury
- Permanent impairment of a body structure or a body function
- The need for in-patient care or prolongation of hospitalization
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Planned hospitalization for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event.

Device-Related Adverse Event (DRAE)

An adverse event related to the use of an investigational medical device. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any malfunction of the investigational device. This definition also includes any event resulting from user error or from intentional misuse of the investigational device.

Serious Device-Related Adverse Event (SDRAE)

Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above.

Unanticipated Adverse Device Effects (UADE)

Any adverse device effect which, by its nature, incidence, severity or outcome, has not been identified in Section 2.3.2.

Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling. Device deficiencies resulting in SADEs will be managed as detailed in Section 2.3.3.

Severity Definitions

The following definitions will be used to determine the severity rating for all adverse events:

Mild: awareness of signs or symptoms, that does not interfere with the subject's usual activity or is transient that resolved without treatment and with no sequelae.

Moderate: a sign or symptom, which interferes with the subject's usual activity.

Severe: incapacity with inability to do work or perform usual activities.

2.3.2. Anticipated Adverse Events

The following are anticipated adverse events related to the device and procedure that will be documented:

Table 1: Anticipated Adverse Events

Event	Comment	Consequence
Aspiration pneumonia	During procedure	Treat with antibiotics at the discretion of PI
Nausea, vomiting, abdominal pain, abdominal spasms, hiccups, heartburn, belching	all expected symptoms that can occur in varying degrees in almost all balloon patients	Mild dehydration Occasionally requires IV hydration
Blood tinged vomitus	Small amounts less than a tablespoon	None
Vomiting blood	Large amounts due to esophageal tear – "Mallory-Weiss Tear" - or due to ulcer of esophagus or stomach.	Requires balloon extraction and possible endoscopic clips to close tear or stop bleeding from ulcer
Superficial mucosal bleed	Tongue, esophagus or stomach during procedure	Small amounts – evaluated by PI and generally not clinically significant

Event	**Comment**	**Consequence**
Heartburn, acid reflux	Treated with medications (PPI, antacids, metoclopramide, sucralfate)	If uncontrolled, balloon down volume adjustment can help
Diarrhea	Due to bacterial overgrowth-like syndrome. Occurs in 20% of subjects and may recur	Treat with metronidazole 500 mg 3 times daily for 5 days
Esophageal or stomach ulcer	Superficial ulcers can be treated with medications (PPI, antacids, sucralfate)	Larger ulcers may require balloon extraction. Small ulcers may be treated with medication and down adjustment of the balloon (Spatz only)
Esophageal tear	During implantation or extraction	May require endoscopic clips
Balloon deflation	Urine turns blue alerting subject to deflation	Deflated balloon will remain in stomach or pass in bowels uneventfully. Rarely the balloon will obstruct intestine
Bowel Obstruction	Deflated balloon that obstructs intestine on its way out	Requires endoscopic extraction or surgery
Perforation of esophagus	Dr error- Balloon inflated in esophagus, or perforation during extraction	Requires endoscopic clips or surgery
Perforated stomach	Spontaneous ischemic perforation or perforated ulcer	Requires endoscopic clips or surgery
Spontaneous Hyperinflation	Unexpected dilation of balloon with air/fluid level in balloon	Spatz: Requires balloon drainage (with culture of fluid) and re-inflation with new fluid (50 ml more than original fluid volume) + Fluconazole 100 mg + Cipro 500 mg within the balloon but without methylene blue. Orbera: Requires balloon extraction
Pancreatitis	Inflammation of the Pancreas	Pain, nausea and vomiting which can be treated with balloon down adjustment (Spatz) or extraction (Orbera)

The investigator will document the clinical significance of all abnormal laboratory findings in the source documents throughout the study. The investigator will exercise his/her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. However, if in the opinion of the investigator, the frequency or severity of the event is greater than would be expected then it must be reported as an AE.

2.3.3. Procedures for recording adverse events

It is the responsibility of the local investigator to ensure that all adverse events (AEs, ADEs, and device deficiencies) occurring during the course of the study are recorded. This may include but not be limited to:

- A description of the event
- The dates of the onset and resolution
- Action taken
- Outcome
- Initial assessment of relatedness to the device
    a. Whether the AE is serious or not
    b. Whether the AE arises from device deficiency
    c. Whether the AE arises from user error

Adverse events that occur during the course of the study should be treated by established standards of care that will protect the life and health of the study subjects

It is the responsibility of the local investigator to collect all directly observed adverse events and all adverse events spontaneously reported by the subject. In addition, each subject should be questioned about adverse events at each visit. Adverse events should be recorded on provided serious adverse event data collection forms.

2.3.4. Reporting Procedures for Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to ensure that all adverse events which fall into the categories of SAEs, DRAEs, SDRAEs and any device deficiencies are reported to the IRB/Ethics committee as soon as possible after becoming aware of the event but no later than 10 working days using the provided SAE form.

2.4. Study Suspension or Early Termination

2.4.1. General

The Investigator or IRB/Ethics committee may recommend suspension or termination of the study for significant and documented reasons. If suspicion of an unacceptable risk to subjects arises during the study, or when so instructed by the IRB/Ethics committee or regulatory

authorities, the Investigator shall suspend the study while the risk is assessed. The Investigator shall terminate the study if an unacceptable risk is confirmed.

2.5. Protocol Deviations

All protocol deviations will be documented with the subject number and date of the protocol deviation. The following information will be documented for each protocol deviation:

- Inclusion/Exclusion exceptions or violations, including subject did not sign informed consent prior to study admission
- Follow-up visit not performed or Follow-up outside of window
- Required testing or questionnaire not performed

3. STATISTICS

3.1. Description of Statistical Methods

3.1.1. Study analyses

Primary Endpoint

Primary Hypothesis and Endpoint

The primary endpoint will be Total Body Loss (TBL) at 12 months. The primary hypothesis and testing method are as follows:

$$H_O: \mu_S - \mu_O \leq 0$$

vs.

$$H_A: \mu_S - \mu_O > 0$$

where μ_S is the mean %TBL in the Spatz3 group at 12 months post implantation and μ_O is the mean %TBL in the Orbera group at 12 months post implantation.

Missing 12-month TBL will be imputed through a multiple imputation process. An analysis of variance model will be fit, including %TBL at 12 months as dependent variable, and effects for treatment group, and study site. A one-sided upper 97.5% CI for the difference between Spatz3 and Orbera least square means will be estimated. If the lower bound of this CI is greater than zero, the null hypothesis will be rejected.

Sample size

Based on the Spatz3 pivotal study, the observed mean %TBL at 12 months among subjects treated with Spatz3 is expected to be 13% with 7.2% standard deviation. The observed %TBL mean in the Orbera group is expected to be 65% of the reported Orbera 6-month %TBL, or 6.6%, with a standard deviation of 6.6%. Based on these assumptions a total sample size of 40 subjects randomized 1:1 (20 in the Spatz3 group and 20 in the Orbera group) will provide 80% power to demonstrate superiority at a one-sided significance of 2.5%. To account for a potential dropout rate of 10%, the final total sample size is 44 subjects randomized 1:1.

3.2. Safety

All adverse events and all serious adverse events will be summarized as the first occurrence for each subject. These adverse events will also be presented by causality. In addition, the number and percent of subjects with balloon deflation will be summarized. Data Collection and Management

3.3. Data Recording

The investigator will be authorized to review and sign each CRF. Data will be input by the dietician. The database will reside at the PI's office.

3.4. Source Data

Source documents include all information obtained in the study. This includes medical records, surgical procedural information, all clinic visits and any supporting information related to a device malfunction or adverse event. Source documents are where data are recorded. All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

The list of standardized case report forms are provided in ***Appendix B*** of this protocol. Information regarding the relevant patient history and physical examination will be obtained from the medical chart and recorded. Study data will be stored and analyzed in an anonymous fashion (no patient identifiers).

3.5. IRB approval

This protocol and associated documents will be submitted for approval by the host institution. Before the study can begin, the investigator must have written evidence of IRB/Ethics committee approval.

Once approval has been granted, the Investigator is responsible for ensuring that he/she complies with the terms of the approval, namely with adverse event reporting, notification of amendments, interim, annual and final reports on the progress of the study.

3.6. Protocol amendments

Any change or addition to this study protocol which may impact on the conduct of the study, potential benefit to the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal written amendment to the study protocol.

All amendments to the protocol will be submitted as appropriate to the IRB/Ethics committee. Approved amendments will be circulated promptly to all investigators by the coordinating center.

3.7. Reporting

3.7.1. Investigator Reports

The following reports are required by the Investigator.

Unanticipated Adverse Device Effects

The Investigator must report the results of an evaluation of an unanticipated adverse device effect to IRB/Ethics committee within 10 working days after the adverse effect.

Progress Reports (or Annual Reports)

The Investigator must provide progress reports annually to IRB/Ethics committee.

Recalls and Device Disposition

The Investigator must notify IRB/Ethics committee of any request of a device return, repair, or dispose of any unit of an investigational device. The notice must be made within 30 working days after the request is made and must state why the request was made.

Deviations from the Investigational Plan

The investigator must notify the IRB/Ethics committee of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. The notice must be provided as soon as possible but no later than 5 working days after the emergency occurred. If it is not an emergency, prior approval from the IRB/Ethics committee is required for changes in or deviations from the investigational plan. If the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety or welfare of the subject, the Investigator is required to obtain prior IRB/Ethics committee approval.

Other Reports: The investigator must provide accurate, complete, and current information about any aspect of the investigation upon request from the reviewing IRB/Ethics committee.

Final Report

The Investigator must notify IRB/Ethics committee within 30 working days of the completion or termination of the investigation. The Investigator must also submit a final report to /Ethics committee within 6 months after the completion or termination of the investigation.

3.8. Participant confidentiality

All study-related information will be stored securely both at the study sites and the coordinating center. All documentation and specimens will be identified by a unique study ID number to

maintain participant confidentiality. Where this is not possible (e.g. informed consent forms), these will be stored separately from any study records identified by the unique study ID.

Participant's information will not be released outside of the study without the written consent of the participant, except as necessary by regulatory authorities.

4. DISSEMINATION POLICY

4.1. Data analysis and release of results

By conducting the study, the investigator agrees that all information provided by the coordinating center will be maintained by the local investigator and the site personnel in strict confidence.

Signatures:

MUDr. Evžen Machytka, Ph.D.

Digitálně podepsal MUDr. Evžen Machytka, Ph.D.
Datum: 2021.07.07 17:45:11 +02'00'

Jeffrey Brooks, MD

Dr Ev Machytka