Title Page

Clinical Investigational Plan (CIP) INFORMATION	
Title:	Evaluation of EndoZip™ System (AS) in Obese Patients who failed to reduce weight with non-surgical weight-loss methods
CIP Number:	**CL00003**
Version Date:	January 13, 2021
Revision:	1.0
Sponsor:	NiTiNotes Ltd. Address: 5 Haeshel st., PO box 3158, Caesarea, Israel Tel: +972-4-8876698 Fax: +972-4- 8864385

Summary of Changes to CIP			
Revision	**Section**	**Description of Change**	**Reason for Change**
NA	NA	NA	NA

1.0 Signature Page

Principal Investigator Signature Page

Title:	Evaluation of EndoZip™ AS System in Obese Patients
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I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement.

_____ _____ _____

Name Signature Date

Sponsor representative signature

Hagit Ephrath

VP QA, Regulatory and Clinical Affairs

_____ _____ _____

Name Signature Date

2.0 Table of Contents

3.0 Protocol Synopsis

Protocol Number	CL00003
Protocol Title	Evaluation of EndoZip™ System (AS) in Obese Patients who failed to reduce weight with non-surgical weight-loss methods
Study Sponsor	NiTiNotes, 5 Haeshel st, P.O Box 3158, Caesarea 3079815, Israel Tel: +972 (4) 8876698 Fax: +972 (4) 8864385
Sponsor Representative	Hagit Ephrath VP QA, Regulatory and Medical Affairs
Study Type	**Pilot study**
Study Product	**EndoZip™ System (AS)**
Study Location	Europe, Israel
Study Centers	1. Hospital Universitario HM Sanchinarro, Madrid, SPAIN 2. Fondazione Policlinico Universitario Agostino Gemelli IRCCS (CERTT), Rome, Italy 3. Rabin Medical Center, Petah Tikva, Israel

Investigators	1. Prof. Gontrand Lopez-Nava 2. Dr. Ivo Boškoski 3. Dr. Steven Shamah
Study Duration	The duration for each participant will be 12 months; the total study duration is expected to be approx. 18 months
Study Design	The study is planned as a multicenter, prospective, single-arm, open-label, controlled clinical trial.
Planned Follow-Up Visits	• Office visits: 1 week, and 1, 2, 4, 6, 8, 10, and 12 month(s) • Remote follow up (by Phone): 3, 5, 7, 9, and 11 month(s) • Endoscopy follow up: 2 and 6 months • Motility evaluation by Gastric Emptying Breath Test (GEBT): 6 months • Physical examination, vital signs, waist circumference and BMI: 1 week, 1, 2, 4, 6, 8, 10 and 12 months • Blood tests: 2, 6 and 12 months • IWQOL-Lite: 2, 6 and 12 months • Sleep Apnea (only for the relevant population): 2, 6 and 12 months
Patient Population	Male and Female with obesity, BMI of 30-40 kg/m^2, between the ages of 21 and 70 who failed to reduce weight with non-surgical weight-loss methods
Planned # of Patients	Up to 45 patients
Planned # of Sites	Up to 5 clinical sites
Planned # of Patients per Site	Up to 20

Study Objective	The objective of this study is to evaluate the safety and effectiveness of the EndoZip system procedure, coupled with lifestyle modifications, for weight reduction in obese patients with BMI of 30-40 kg/m^2.
Study Procedures	*Visit 1: Baseline Screening Visit* • After signing informed consent, patients will be screened for study eligibility by: • Eligibility Criteria • Demographics, Medical history, Obesity History • Physical examination • Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) • Body Weight, Height and Waist circumference • Laboratory evaluations (Hematology, CBC with differential, PTT, PT and INR, Comprehensive Metabolic Panel (Kidney and liver functions – blood glucose, HbA1c, Urinalysis, TSH, fasting lipid panel) • Motility evaluation by Gastric Emptying Breath Test (GEBT) • Influence of Weight on Quality of Life (IWQOL) questionnaire • Psychological health questionnaire-9 (PHQ-9) • Patients with diagnosed Sleep Apnea will be tested using WatchPAT 200
	Visit 2: Procedure Day • Physical examination • Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) • Body Weight, Height and Waist circumference • Pregnancy test • Electrocardiogram (ECG) evaluation • Endoscopy screening procedure

	• EndoZip Procedure • EndoZip's Usability Questionnaire • Meeting with dietitians/nutritionists • AE / SAE
	Phone call follow up At day 1 after patient's discharge to verify the patient's well-being.
	Visit 3: Follow up 1 week after patient's discharge day: • Physical examination • Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) • Body Weight, Height and Waist circumference • Meeting with dietitians/nutritionists - lifestyle modifications counseling • Concomitant medication • AE / SAE
	Visit 4: Follow up 1 month after procedure day • Physical examination • Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) • Body Weight, Height and Waist circumference • Meeting with dietitians/nutritionists - lifestyle modifications counseling • Concomitant medication • AE / SAE
	Visit 5: Follow up 2 months after procedure day: • Physical examination • Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) • Body Weight, Height and Waist circumference • Meeting with dietitians/nutritionists - lifestyle modifications counseling

	• Laboratory evaluations (Hematology, CBC with differential, Comprehensive Metabolic Panel (Kidney and liver functions – blood glucose, HbA1c, Urinalysis, fasting lipid panel) • Endoscopy follow up procedure • IWQOL questionnaire • Concomitant medication • AE / SAE • Patients with diagnosed Sleep Apnea will be tested using WatchPAT 200
	Visit 6: Follow up 6 months after procedure day: • Physical examination • Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) • Body Weight, Height and Waist circumference • Meeting with dietitians/nutritionists - lifestyle modifications counseling Laboratory evaluations (Hematology, CBC with differential, Comprehensive Metabolic Panel (Kidney and liver functions – blood glucose, HbA1c, Urinalysis, TSH, fasting lipid panel) • Motility evaluation by Gastric Emptying Breath Test (GEBT) • Endoscopy procedure • IWQOL questionnaire • Concomitant medication • AE / SAE • Patients with diagnosed Sleep Apnea will be tested using WatchPAT 200
	Visit 7: Follow up 12 months after procedure day: • Physical examination • Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) • Body Weight, Height and Waist circumference • Meeting with dietitians/nutritionists - lifestyle modifications counseling • Laboratory evaluations (Hematology, CBC with differential, Comprehensive Metabolic Panel (Kidney and liver functions – blood glucose, HbA1c, Urinalysis, fasting lipid panel)

	• IWQOL questionnaire • Concomitant medication • AE / SAE • Patients with diagnosed Sleep Apnea will be tested using WatchPAT 200
	Additional follow up visits: Patients will receive brief (30min) telephone calls in the months that do not include in person visits (in months 3, 5, 7, 9, and 11 after the procedure). These counseling sessions are primarily designed to improve adherence to recommendations to consume a healthy diet and increase physical activity to promote weight loss and overall health. Additional in person visits In addition to the visits above, patients will visit the clinic in 4, 8, and 10 months after the procedures. In these visits, patient will meet the physicians and the dietitians/nutritionists. These counseling sessions are primarily designed to improve adherence to recommendations to consume a healthy diet and increase physical activity to promote weight loss and overall health.
Primary Endpoint	The effectiveness of the EndoZip system will be assessed by the following co-primary endpoints: 1. Mean percent of total body weight loss (%TBWL) after 12 months. 2. Percentage of patients with a reduction in %TBWL of at least 5% at 12 months.
Secondary Endpoints	The following secondary endpoints will be evaluated: 1. Percent of excessive weight loss (%EWL) over 6 and 12 months. 2. Reduction of weight and waist circumference over 6 and 12 months. 3. Impact of EndoZip procedure on gastric motility at 6 months. 4. Changes in Weight-related Quality of Life (IWQOL) Questionnaire scores at 6 and 12 months 5. Time analysis including procedure duration, anesthesia duration, patient recovery duration

	6. Change in comorbid conditions over 12 months evaluated by: a. Blood pressure b. Glucose, HbA1c c. Lipid levels (Total Cholesterol, LDL-C, HDL-C, and triglycerides) d. Sleep Apnea 7. Usability evaluation and physician's satisfaction based on a questionnaire
Safety Endpoints	The following safety variables will be recorded at regular intervals during the study: ● Physical examination ● Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) ● Telemetry monitoring (continuous ECG, respiratory rate, SpO2 monitoring) during procedure and at recovery ● Clinical laboratory tests (hematology, clinical chemistry, lipid profile and urinalysis) ● Adverse event (AE) assessments ● Monitoring of sleep apnea (If relevant) Safety will be characterized through a summary of the incidence of adverse events and serious adverse events by relation to study treatment. A Data Safety Monitoring Board (DSMB) will review and adjudicate all serious device related and non-related adverse events and any other events deemed necessary.
Randomization	NA- single arm study
Eligibility Criteria	**Inclusion Criteria** 1. Age 21-70 2. BMI ≥ 30 and ≤40 kg/m². 3. Willingness to comply with the substantial behavioral modifications program as required by the procedure. 4. Patients with history of failure with non-surgical weight-loss methods. 5. Willingness to follow protocol requirements, including signed informed consent, routine follow-up schedule, completing laboratory tests,

completing IWQOL questionnaire and completing the medically supervised diet and behavior modification program.

6. Residing within a reasonable distance from the investigator's office and able to travel to the investigator to complete all routine follow- up visits.
7. Ability to give informed consent.
8. Women of childbearing potential (i.e., not post-menopausal or surgically sterilized) must agree to use adequate birth control methods.

Exclusion Criteria

1. Prior surgery of any kind on the gastrointestinal tract (except uncomplicated cholecystectomy or appendectomy).
2. Patients with history of small bowel or colonic obstruction, and/or adhesive peritonitis and/or abdominal adhesions.
3. Patients with any inflammatory disease
4. Patients with history of cancer in the gastrointestinal tract.
5. Potential upper gastrointestinal bleeding conditions such as a history of angioectasias.
6. A known gastric mass or gastric polyps > 1 cm in size.
7. Patients with TG >500 or LDL >190
8. A known hiatal hernia > 4cm of axial displacement of the z-line above the diaphragm or severe or intractable gastro-esophageal reflux symptoms while on maximal medical therapy.
9. A structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of the endoscope.
10. Patient with motility disorders of the GI tract or intractable constipation
11. Patients with known coagulation disorder (INR >1.5) or on anticoagulation therapy.
12. Type 1 diabetes or Type 2 diabetes with a HgbA1c >8 in 6 weeks prior the procedure or use of any medication for diabetes other than metformin. Patients with any serious health condition unrelated to their weight that would increase the risk of endoscopy
13. Patients with chronic abdominal pain
14. Patients with hepatic insufficiency or cirrhosis
15. Patients that used an intragastric device for weight loss within 2 years prior to this study.

	16. Patients with psychological health questionnaire-9 (PHQ-9) score of 10 or higher. 17. Patients receiving daily prescribed treatment with high dose aspirin (> 100mg daily), anti-inflammatory agents, anticoagulants or other gastric irritants. 18. Patients with history or current abuse of drugs or alcohol 19. Patients who are unable or unwilling to take prescribed proton pump inhibitor medication 20. egg, milk, or wheat allergy (unable to go through the GEBT) 21. Patients who are pregnant or breast-feeding. 22. Patients who are taking medications that cause weight loss 23. Patients with Severe cardiopulmonary disease or other serious organic disease which might include known history of coronary artery disease, Myocardial infarction within the past 12 months, poorly-controlled hypertension, required use of NSAIDs 24. Patients taking medications on specified hourly intervals that may be affected by changes to gastric emptying, such as anti-seizure or anti-arrhythmic medications 25. Patients who are taking corticosteroids, immunosuppressants, and narcotics 26. Symptomatic congestive heart failure, cardiac arrhythmia or unstable coronary artery disease. 27. Pre-existing respiratory disease such as chronic obstructive pulmonary disease (severe COPD), pneumonia or cancer. 28. Diagnosis of autoimmune connective tissue disorder (e.g. lupus, HIV, erythematous, scleroderma) or immunocompromised. 29. Specific diagnosed genetic disorder such as Prader Willi syndrome (motility disorder) 30. Eating disorders including night eating syndrome (NES), bulimia, binge eating disorder, or compulsive overeating 31. Known history of endocrine disorders affecting weight such as uncontrolled hypothyroidism.
Statistical Considerations	

Analysis Populations	Full Analysis Set (FA): includes all enrolled patients, excluding the patients who enrolled in the run-in period, who undergone EndoZip procedure. Modified Full Analysis Set (mFA): The modified full (mFA) analysis set will include all patients who have at least one post initiation follow up visit and met the study Eligibility Criteria. Per-Protocol (PP) analysis set: includes all patients from the mFA set who do not have any major protocol violations. Statistical Analysis of Analysis Sets Safety assessments will be performed on the FA analysis set. The mFA will serve as the principal data analysis set for the primary and secondary statistical efficacy endpoints. The primary, secondary efficacy assessment will also be performed on the PP and FA cohorts for descriptive purposes and to show consistency of study results.
Sample Size Estimation	This is a pilot study that will include up to 45 patients; no statistical considerations were made to determine the sample size.
Statistical Analyses	***General Methods:*** Statistical analyses will be mainly descriptive in nature. Any statistical tests if performed will be two-sided, unless otherwise stated. Study data will be summarized with descriptive statistics and presented in tables and figures. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum and categorical variables by a count and percentage. If multiple measurements are taken in a single patient, statistics described below will be appropriately modified to accommodate the within patient correlation. Any deviation from specified statistical plan will be in addition to "per protocol" analysis and will be reported as such Post-hoc analysis will be conducted according to the existing data gathered, if necessary. ***Handling of the Type I Error***

The overall significance level for this study is 5%, confidence intervals will be two-sided using a 95% confidence level, except for treatment by site interaction that will be tested at a significance level of 10%.

Primary Endpoints

The %TBWL at each visit will be calculated as 100*(Weight(BL) -Weight(Visit))/ Weight(BL), where weight is measured in kilograms. %TBWL will be summarized with descriptive statistics at each follow-up visit.

%TBWL will be evaluated by using repeated measures analysis of covariance (ANCOVA MIXED model). Baseline weight, center and visit will be used as covariates. Baseline weight will be entered as a continuous variable so that the potential for co-linearity problems will be minimized.

The unstructured covariance matrix structure will be used. If the model doesn't converge, then either the compound symmetry or autoregressive (whichever model has the lower AIC statistic) covariance matrix structure will be used instead. For this evaluation, no imputation of missing data is considered beyond the model estimates.

The model estimated mean %TBWL at each visit will be presented with 95% confidence interval and level of significance.

A count and percentage of patients achieving at least 5% TBWL will be presented with exact 95% confidence interval.

Subset Analysis of the primary endpoint:

Additionally, the %TBWL median, mean and standard deviation and percent of patients with greater than 5%TBWL will be summarized. Covariates may include demographic data (sex, age, BMI) or other baseline characteristics.

Secondary Endpoints

Excess Weight Loss % (EWL%)

EWL% of patients at 1, 2, 6 and 12 month(s) by study group will be summarized with descriptive statistics with 95% confidence intervals.

The percent excess weight loss (%EWL) will be calculated as (Weight(BL) – Weight(Visit)/ ExcessWeight(BL), where ExcessWeight(BL) is calculated as difference

	between the patient's baseline weight in kilograms and the kilograms at which the patient's BMI would be 25. **Change of Weight and Waist Circumference Over 12 Months from Baseline** Change from baseline in BMI at 1, 2, 6 and 12 month(s) by study group will be summarized with descriptive statistics with 95% confidence intervals. **Changes in Weight-related Quality of Life (IWQOL) Questionnaire at 12 months** IWQOL questionnaire records will be summarized by study groups will be summarized with descriptive statistics with 95% confidence intervals. **Time analysis** Time analysis including procedure duration, anesthesia duration, patient recovery duration will be evaluated and will be summarized with descriptive statistics with 95% confidence intervals

4.0 Acronyms and Definitions

ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
ASADE	anticipated serious adverse device effect
CRF	case report form
CIP	clinical investigation plan
CRO	contract research organization
COTS	commercial off the shelf
CA	competent authority
DSMB	data and safety monitoring board
EC	European commission
ESD	endo-Surgery Device
FA	full analysis (data set)
FDA	food and drug administration
GEBT	gastric emptying breath test
GCP	good clinical practice
GLP	good laboratory practice
IB	investigator's brochure
ICF	informed consent form

ICH	international Conference on Harmonisation
IEC	institutional ethics committee
IFU	instruction for use
IRB	institutional review board
ISF	investigator site file
ISO	international organization for standardization
mFA	modified full analysis (data set)
NCA	national competent authorities
PI	principal investigator
PP	per protocol (data set)
RA	regulatory authorities
SADE	serious adverse device effect
SAE	serious adverse event
SOP	standard operating procedure
USADE	unanticipated serious adverse device effect

5.0 Introduction

This document is a protocol for human research study. This study will be conducted in accordance with the applicable international standard of Good Clinical Practice, and institutional research policies and procedures.

5.1 Background

5.1.1 Applicable epidemiological background

Obesity is a global epidemic. In the last few decades, obesity has gained significance as a worldwide health problem. The World Health Organization (WHO) estimated that approximately 1.5 billion adults (age 20 y or older) were overweight [1]. Currently, more than 30% of the US adult population is obese [2], which accounts for approximately 72 million obese Americans [3].

The morbidity associated with obesity is alarming serious health concern, with an increased incidence of metabolic syndrome, type 2 diabetes mellitus, hypertension, and many other comorbidities.

5.1.2 Available treatment modalities

There are several alternatives to for the treatment of obesity (BMI of >30 kg/m^2), which can be divided into the following: non-surgical treatments, medical devices, and surgery. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his or her physician to select the method that best meets expectations and lifestyle.

Non-Surgical Treatments

Non-surgical treatments for obesity include:

- Diet, exercise, and behavioral modifications, and
- Prescription weight loss medications.

Several reports have suggested a rather high incidence of failure for obese patients to sustain long-term weight loss with any form of non-surgical treatment.

Intra-Gastric Balloons

Intra-gastric balloons are typically recommended for patients with a BMI 30-40 kg/m^2. It is a temporary non-surgical obesity treatment that induces short-term weight loss by placing a soft, elastomeric balloon in the stomach, thus partially filling the stomach to achieve satiety. The Balloon is removed 6-12 months after placement.

Obesity Surgery

Bariatric surgery is typically recommended for patients with a BMI of at least 40 kg/m^2,

or a BMI of at least 35 kg/m^2 with one or more obesity-related comorbid conditions. The most common types of bariatric surgery are described below.

Roux-en-Y Gastric Bypass (RYGB)
In a gastric bypass, the surgeon first constructs a proximal gastric pouch and then creates an outlet from the pouch to a limb of the small bowel. This results in a bypass of most of the stomach and duodenum.

Vertical Sleeve Gastrectomy
Vertical sleeve gastrectomy is a procedure which reduces the size of the stomach by surgical removal of a large portion of the stomach. The open edges are then sutured together to form a sleeve. The size of the stomach is permanently reduced without bypassing the intestines. Unlike RYGB, the stomach is not bypassed and there is no malabsorption component.

Biliopancreatic Diversion Duodenal Switch
The biliopancreatic diversion with duodenal switch is a procedure in which stomach removal is restricted to the outer margin, leaving a stomach sleeve with the pylorus intact. The small intestine is divided with one end attached to the stomach pouch. The majority of the small intestine is bypassed.

Single Anastomosis (Omega Loop) Bypass "mini bypass"
The mini bypass is a procedure in which the surgeon will reduce the size or volume of the stomach, similar to the gastric sleeve. This sleeve is then connected to the intestine, bypassing up to 200cm of the upper part of the intestine.

In general, bariatric surgeries have shown, in multiple studies, to lead to significant and durable weight loss. However, it has been estimated that only 1% of eligible patients undergo bariatric surgery because of serious complications including perforation, hemorrhage, infections and bowel obstructions, limited access, cost, and patient preference [4].

5.1.3 Study Rationale

NiTiNotes Ltd. has developed the EndoZip System which offers obesity treatment by an operator-friendly endoscopic procedure generating an endoluminal gastroplasty that restricts the stomach and impairs motility.

The EndoZip system is designed to allow for the creation of multiple internal gastric segmentations in the stomach by using an endoscopic approach. The system allows the forming of wall-to-wall longitudinal attachments of the anterior and posterior stomach walls, creating multiple plications within. Another important determinant which predicts a favorable safety outcome is the minimally invasive nature of the procedure.

The pre-clinical studies and initial human study (details are provided in 6.2 and 6.3), using an earlier configuration of the device, have proven to have excellent safety profile, and provided initial performance data.

The aim of this study is to evaluate the updated device configuration of EndoZip system to establish the long-term safety and further validate the efficacy claim in the intended population.

6.0 Investigational Device

6.1 General Description

The EndoZip™ is an automatic, operator-friendly Endo-Surgery Device (ESD) designed to create multiple internal gastric segmentations in the stomach by using an endoscopic approach. The system applies a wall-to-wall longitudinal attachment of the anterior and posterior stomach walls, creating multiple plications within.

The EndoZip is inserted to the stomach through a standard endoscopy designated Overtube. The device advancement and positioning in the stomach is visually guided by a small diameter endoscope inserted through device's dedicated channel. In addition, EndoZip is connected to a COTS (Commercial Off the Shelf) vacuum pump used in Endoscopy units / clinics.

The system with the aid of the external vacuum pump, enables the approximation of the opposite stomach walls by extracting air from the chosen deployment site, i.e., the creation of a near vacuum state, causing the tissue segments to draw into the Bougie and create a narrowing for segmentation of the stomach.

Following the approximation process, a custom designed needle is driven through the Bougie, (from its distal end toward it proximal end), passing the attached suture through the approximated tissue segments and creating the continuous plications within the stomach. Then the device enables tightening and cinching the approximated tissue segment with an integrated, dedicated clip. The procedure is completed with device retraction from the deployment site and a visual confirmation using a scope. The system provides suturing stage indication by a LED bar located in the device handle.

Per the IFU, up to five (5) systems, per the physicians' judgement, may be used for the creation of multiple plications within the stomach. For the purpose of this study up to six (6) systems, per the physicians' judgement, may be used for the creation of multiple plications within the stomach.

The EndoZip™ System is made of biocompatible non absorbable materials widely used as surgical sutures. The system is supplied sterile.

In addition, the EndoZip™ System is a minimally invasive procedure, a reproducible and easy to use device that can aid the obesity treatment by expanding the access and acceptability to a broad population segment.

6.1.1 EndoZip Main components

The EndoZip system consists of a disposable device that controls the procedure and a reusable electrical power supply.

6.1.2 EndoZip Disposable Device

The EndoZip disposable device comprises three main components: Bougie, Insertion Tube and Handle as depicted in Figure 1 below.

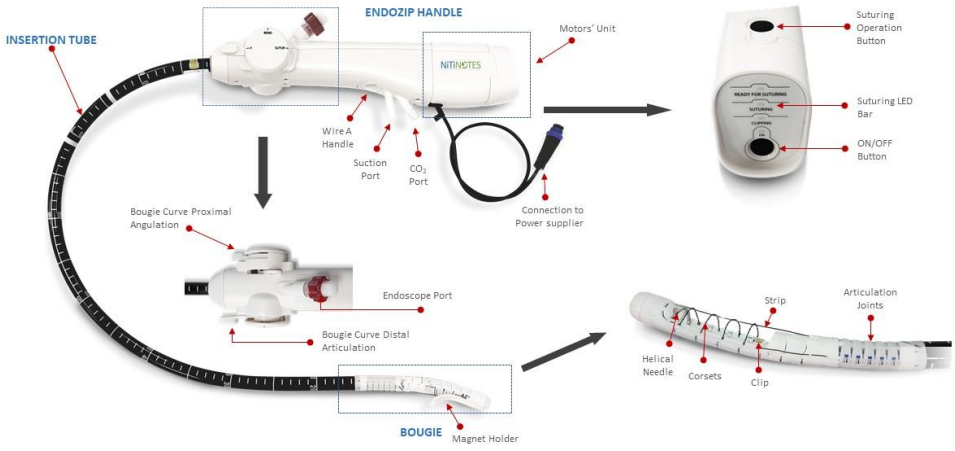


Figure 1 – EndoZip Disposable Device

Bougie

The distal end of the device, referred as the "Bougie", is designed to optimize the suturing mechanism. It contains a chamber that captures the tissue using a vacuum, to support full-thickness sutures. In addition, the Bougie includes a steerable segment that facilitates device maneuvering.

Insertion Tube (IT)

The Insertion Tube (IT) connects the Handle and Bougie parts, supporting insertion and evacuation of air and CO_2. It also contains a channel for the endoscope passthrough.

EndoZip Handle

The EndoZip handle aids the physician to maneuver the device and position it in the desired abdominal area. In addition, it controls all suturing activity. The handle comprises 2 functional parts:

- Motor unit: Includes motors and controllers to perform all required activities including stitching, tightening, clipping, and cutting of suture wire. The unit has a sensing mechanism that ensures that the stages after stitching are contingent upon the needle reaching its designated area.

- Mechanical control unit: The mechanical control unit aids the physician to maneuver the device and position it in the desired abdominal area.

In addition, the EndoZip System comprises the following **Disposable Components**:

- pinch clamps – 2 pinch clamps used to manage the vacuum via the EndoZip and the endoscope during the procedure.

- Sealing Adaptor – A component located between the EndoZip system to the Overtube.

6.1.3 EndoZip Electrical Power Supply (Reusable)

The EndoZip electrical power supply contains a unique and dedicated connector to the EndoZip disposable.

The EndoZip System complies with the IEC 60601-1 Ed. 3.1, 60601-1-6 Ed. 3.0 safety standards and IEC 60601-1-2 EMC standard.

For detailed description of the device please refer to the current version of the study Investigator's Brochure (IB).

6.2 Pre-clinical data

Several bench tests were performed with the EndoZip™, to ensure that the device meets its design specifications and is safe for its intended use. Performance of the device was also evaluated, especially the mechanical properties, functional features and operational parameters.

NiTiNotes conducted animal studies during the first prototype development to evaluate the safety of the EndoZip system under in-vivo conditions. A swine model was chosen as it has been used extensively as a gastrointestinal model due to its anatomic and physiologic characteristics which are similar to humans. Notably, despite being the best model animal for human, the swine model may be very challenging and represents the worst-case scenario for this study as the swine's gastric capacity and surface tension are significantly greater compared with humans.

In this experiment, that included application of the system and suturing it was proven that the system is capable to perform approximation of the stomach tissue segments (Anterior and Posterior segments) and to suture said segments one to the other using a continuous suturing. Furthermore, EndoZip™ was considered non-irritant as expected in histological evaluation and a normal reaction to such a suture was observed in the procedure surroundings. Unexpected adverse reactions were not observed.

Although studies were performed on an earlier prototype device, the conclusion are valid to the final device as both configurations (i.e., prototype and final design) share similar suturing mechanism of action, meaning gripping and holding the tissue in the Bougie chamber using vacuum, and same needle, suture thread and clips' materials.

All components of the EndoZip™, that come in direct contact with the patient, were deemed biocompatible in accordance with the ISO 10993 biocompatibility standards.

For in-depth review of the pre-clinical investigations, please see the study Investigator's Brochure (IB).

6.3 Clinical data to Date

One clinical study has been conducted to date. The study was designed to evaluate the safety and the outcomes of the EndoZip prototype system with respect to obese patients' weight loss in 6 months. It was a single arm, prospective single center study, conducted by Prof. Lopez-Nava at the Bariatric Endoscopy unit of HM Sanchinarro University Hospital, Madrid, Spain. The institutional review board approved the study. The study was conducted in accordance with the ethical principles detailed in the

Declaration of Helsinki and was consistent with Good Clinical Practices recommendation (Clinicaltrials.gov, NCT03472196). The study results were published on January 2020 at Obesity Surgery Journal [OBES SURG (2020) 30:1696–1703].

Study Design - Patients in this study were instructed to be on a liquid diet and fast a day prior the procedure. BMI, waist circumference, blood tests and a Quality of life questionnaire were recorded prior the procedure.

Patients were followed up 7-10 days, 6 weeks, 3 and 6 months after the procedure. In the follow up visits, changes in the patients' well-being, blood tests outcomes, compliance with the diet instructions and weight were recorded. At 6 weeks, 3 and 6 months after the procedure, presence and location of the stiches by means of endoscopy, and quality of life were recorded.

Results - Eleven obese class I and II patients are included in this analysis.

The age range of the patients was 35-51 years, their average weight was 111.1 kg, their average height was 174 cm and their BMI (kg/m^2) ranged from 30.2-39.7.

Thirty-one (31) procedures were applied in 11 patients. All procedures (100%; 95% CI [89%,100%]) were completed successfully.

All eleven patients reached 3-months and adhered until 6-month follow-up. The mean ±SD TBWL at 3-month and 6-month was 14.8 ± 4.8 Kg and 17.8 ± 6.7 Kg, respectively ($p<0.001$). The mean ±SD %TBWL at 3-month and 6-month was 13.5 ± 4.7% and 16.2 ± 6.0%, and the mean ±SD %EBWL was 46.5 ± 28.6% and 54.3 ± 28.4%, respectively.

The mean ±SD of waist circumference at baseline was 117 ± 9.4 and significantly ($p<0.001$) reduced 6 months after the EndoZip procedure to mean ±SD of 100 ± 12.7.

Safety evaluation - There were no adverse events related to the study. Two events unrelated to the device and / or EndoZip procedure occurred during the study.

6.3.1 Additional Information

For the completeness of this section it should be noted that in an expansion of the clinical study one technical failure, where the needle did not penetrate through the tissue smoothly and could not be retrieved, per the IFU instructions, from the stomach. The needle was retrieved endoscopically, and the patient received antibiotics to prevent any infection. The event has

resolved with no clinical sequelae. The event was classified as an anticipated and resolved serious adverse event. This event lead to a redesign of the Bougie portion of the device configuration.

These and all other changes implemented in the improved device configuration (i.e., final device) were verified and validated in the bench testing mentioned above.

7.0 Benefit - Risk Assessment

7.1 Potential Benefits

EndoZip™ System is an automatic, operator-friendly ESD that allows the user to create multiple internal gastric segmentation in the stomach by using an endoscopic approach. The System generates an endoluminal gastroplasty that restricts the stomach and impair motility. Since this is an endoluminal approach, the potential for leaks has been significantly minimized. Also, this procedure is reversible and requires short recovery duration, and thus may be applied to a much wider patient population, by gastroenterologists as well as surgeons.

NiTiNotes has performed several preclinical and clinical studies in the development process with prototypes of varying designs as with the final device configuration.

In a First In Human study including 11 patients and 31 suture procedures, the first EndoZip prototype device presented promising safety and effectiveness results of %TBWL of 16.2 ± 6.0 at 6 months. No SAE related to the study occurred within the study duration. In an extended feasibility study a technical failure occurred and study was early terminated. The final design configuration includes improvements aim to minimize the likelihood of such an event.

The following are potential benefits of the EndoZip™ System stratified by key stakeholders:

Physicians:

- An effective non-surgical, long lasting treatment.
- Facilitate reduction in comorbidities.
- User-friendly procedure that has a minimal learning curve and provides reproducible results (not operator-dependent).
- Can be readily available for in clinic use, thereby improving patient access.
- Lower risk profile while still providing clinically significant weight loss outcomes.
- Short procedure with potential of cost reduction.

Patients:

- Favorable safety profile with minimal trauma.
- Effective non-surgical, long lasting treatment.
- Potentially easier and shorter recovery.

Healthcare System:

- Lower expenditure - Patients are expected shorter recovery and reduced complications
- Procedure can be conducted by endoscopists and surgeons

7.2 Anticipated Risks

The EndoZip system is an ESD, hence the complication associated with using it are anticipated to be similar to other endoscopic suturing devices such as OverStitch™ Endoscopic Suturing System (K181141). As with any intragastric suturing procedure, using the EndoZip System may lead to the following potential risks:

1. Severe tissue trauma that requires operation (e.g., perforation, obstruction, unscheduled implant removal due to severe pain or other symptoms, etc.).
2. Severe patient infection / biologic reaction that requires intensive care unit treatment.
3. User electric shock/injury hazard/Fire.
4. Moderate tissue trauma that requires therapy other than a surgical operation (e.g., ulcer, GI bleeding, GERD, etc.).
5. Minor patient infection / biologic reaction.
6. Minor user infection / biologic reaction.
7. Minor tissue trauma and/or patient discomfort that can be managed with prescription drugs and / or mild intervention (e.g., dehydration, cutaneous bleeding, laceration, esophagitis, gastritis, severe vomiting, etc.).
8. Extended procedure time.
9. Failed procedure.
10. Equipment damage to endoscope.

11. Patient discomfort (e.g. nausea, vomiting, bloating, cramps, diarrhea, constipation, etc.).
12. User injury hazard.
13. User inconvenience.

All risks of using EndoZip were mitigated by design and verification tests. NitiNotes' risk management process complies EN ISO 14971:2019. The potential residual risk following the mitigations are all acceptable (for more details please refer to "Risk analysis report").

As described in the following section, the device's benefits outweigh these risks.

7.3 Benefit – Risk Assessment

The EndoZip™ System is expected to provide significant weight loss outcomes including responder rate, defined as ≥5%, of at least 50% at 12 months. In addition, the EndoZip™ System is a minimally invasive procedure, a reproducible and easy to use device that can aid the obesity treatment by expanding the access and acceptability to a broad population segment. The expected risks associated with the system use may require, at most, surgical or endoscopic intervention, thus safety profile meets the low to moderate risk. The EndoZip™ System is designed to minimize these risks. In addition, the company applied the relevant special control activities to ensure that the system performs in accordance with its performance specifications. Thus, it is reasonable to conclude that the device's benefits will outweigh its risks.

8.0 Study Objectives

8.1 Primary objectives

The evaluate the safety and effectiveness of the EndoZip system procedure, followed by lifestyle modifications, for weight reduction in obese patients with BMI of 30-40 kg/m^2.

8.2 Secondary objectives:

- To evaluate the potential improvement in patients' conditions.
- To evaluate the duration related to the EndoZip procedure.
- To evaluate physicians' satisfaction related to the EndoZip usability.

9.0 Study Endpoints

9.1 Primary endpoints

The effectiveness of the EndoZip system will be assessed by the following co-primary endpoints:

1. Mean percent of total body weight loss (%TBWL) after 12 months.
2. Percentage of patients with a reduction in %TBWL of at least 5% at 12 months.

Safety will be characterized through a summary of the incidence of adverse events and serious adverse events by relation to study treatment.
A Data Safety Monitoring Board (DSMB) will review and adjudicate all serious device related and non-related adverse events and any other events deemed necessary.

9.2 Secondary endpoints

The following secondary endpoints will be evaluated:

1. Percent of excessive weight loss (%EWL) over 6 and 12 months.
2. Reduction of weight and waist circumference over 6 and 12 months.
3. Impact of EndoZip procedure on gastric motility at 6 months.
4. Changes in Weight-related Quality of Life (IWQOL) Questionnaire scores at 6 and 12 months.
5. Time analysis including procedure duration, anesthesia duration, patient recovery duration.
6. Change in comorbid conditions over 12 months evaluated by:
    a. Blood pressure
    b. Glucose, HbA1c
    c. Lipid levels (Total Cholesterol, LDL-C, HDL-C, and triglycerides)
    d. Sleep Apnea test
7. Physicians' satisfaction based on a questionnaire

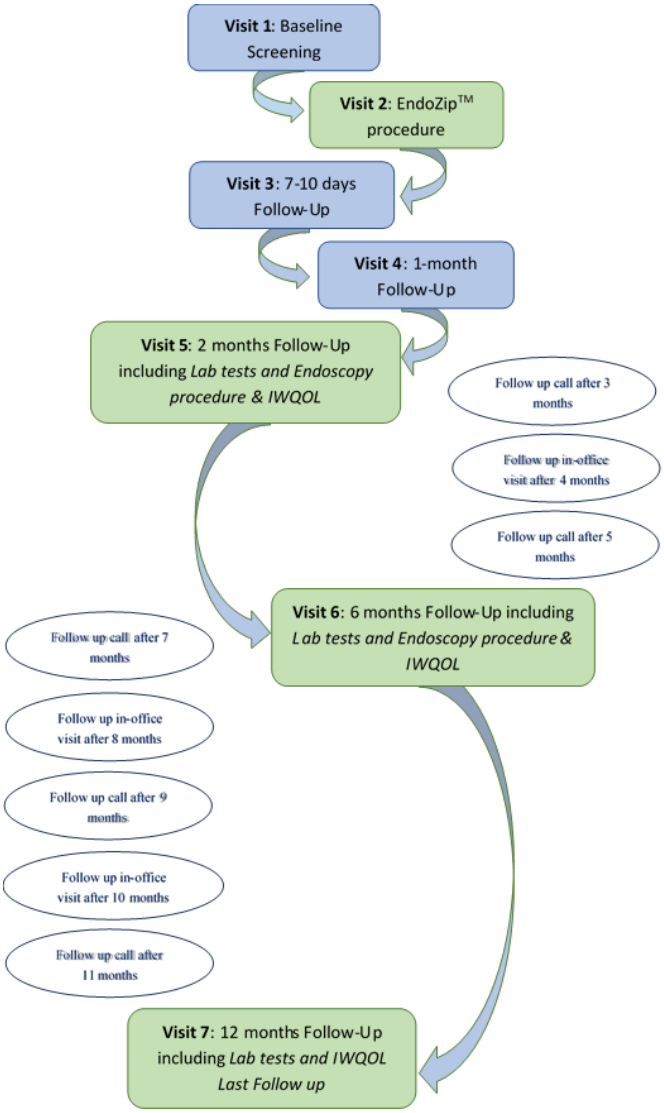
10.0 Study Design

This multicenter, prospective, single arm study will include up to 45 patients (10-20 patients per site), aimed at evaluating the performance of the EndoZip System in obese patients who failed to reduce weight with non-surgical weight-loss methods.

The first two (2) patients in each site will be considered as run-in period, to compensate for any learning curve that may be required for the EndoZip performance evaluation.

Patients will be enrolled at up to 5 clinical sites in Europe and Israel. Patients who meet the eligibility criteria is expected to come the clinic for at least 10 visits.

10.1 Study Flow Chart



11.0 Patient Selection and Enrollment

After being informed of the nature of the study, the patient will sign a written informed consent form (ICF) that has been approved by the appropriate Institutional Ethics Committee (IEC) and regional Competent Authority (CA). Enrollment of up to 45 patients is planned.

Patients will be considered for the study if they meet the specific inclusion/exclusion criteria. The criteria for enrollment must be followed explicitly.

Enrollment completion is expected to take place up to 6 months following IEC approval of the study.

11.1 Inclusion Criteria

1. Age 21-70
2. BMI ≥ 30 and ≤40 kg/m²
3. Willingness to comply with the substantial behavioral modifications program as required by the procedure
4. Patients with history of failure with non-surgical weight-loss methods
5. Willingness to follow protocol requirements, including signed informed consent, routine follow-up schedule, completing laboratory tests, completing IWQOL questionnaire and completing the medically supervised diet and behavior modification program
6. Residing within a reasonable distance from the investigator's office and able to travel to the investigator to complete all routine follow- up visits.
7. Ability to give informed consent
8. Women of childbearing potential (i.e., not post-menopausal or surgically sterilized) must agree to use adequate birth control methods

11.2 Exclusion Criteria

1. Prior surgery of any kind on the gastrointestinal tract (except uncomplicated cholecystectomy or appendectomy).
2. Patients with history of small bowel or colonic obstruction, and/or adhesive peritonitis and/or abdominal adhesions.
3. Patients with any inflammatory disease.
4. Patients with history of cancer in the gastrointestinal tract.
5. Potential upper gastrointestinal bleeding conditions such as a history of angioectasias.
6. A known gastric mass or gastric polyps > 1 cm in size.
7. Patients with TG >500 or LDL >190.
8. A known hiatal hernia > 4cm of axial displacement of the z-line above the diaphragm or severe or intractable gastro-esophageal reflux symptoms while on maximal medical therapy.
9. A structural abnormality in the esophagus or pharynx such as a stricture or diverticulum that could impede passage of the endoscope.
10. Patient with motility disorders of the GI tract or intractable constipation.
11. Patients with known coagulation disorder (INR >1.5) or on anticoagulation therapy.
12. Type 1 diabetes or Type 2 diabetes with a HgbA1c >8 in 6 weeks prior the procedure or use of any medication for diabetes other than metformin. Patients with any serious health condition unrelated to their weight that would increase the risk of endoscopy.

13. Patients with chronic abdominal pain
14. Patients with hepatic insufficiency or cirrhosis
15. Patients that used an intragastric device for weight loss within 2 years prior to this study.
16. Patients with psychological health questionnaire-9 (PHQ-9) score of 10 or higher.
17. Patients receiving daily prescribed treatment with high dose aspirin (> 100mg daily), anti-inflammatory agents, anticoagulants or other gastric irritants.
18. Patients with history or current abuse of drugs or alcohol
19. Patients with known hypersensitivity to Spirulina, egg, milk or wheat allergens (unable to go through the GEBT)
20. Patients who are unable or unwilling to take prescribed proton pump inhibitor medication.
21. Patients who are pregnant or breast-feeding.
22. Patients who are taking medications that cause weight loss.
23. Patients with Severe cardiopulmonary disease or other serious organic disease which might include known history of coronary artery disease, Myocardial infarction within the past 12 months, poorly-controlled hypertension, required use of NSAIDs
24. Patients taking medications on specified hourly intervals that may be affected by changes to gastric emptying, such as anti-seizure or anti-arrhythmic medications.
25. Patients who are taking corticosteroids, immunosuppressants, and narcotics.
26. Symptomatic congestive heart failure, cardiac arrhythmia or unstable coronary artery disease.
27. Pre-existing respiratory disease such as chronic obstructive pulmonary disease (severe COPD), pneumonia or cancer.
28. Diagnosis of autoimmune connective tissue disorder (e.g. lupus, HIV, erythematous, scleroderma) or immunocompromised
29. Specific diagnosed genetic disorder such as Prader Willi syndrome (motility disorder).
30. Eating disorders including night eating syndrome (NES), bulimia, binge eating disorder, or compulsive overeating.
31. Known history of endocrine disorders affecting weight such as uncontrolled hypothyroidism.

11.3 Withdrawal Criteria

Patients may withdraw from the study at their own request or at the request of their legally acceptable representative. The investigator may withdraw a patient from the study at any time for the following reasons:

- Severe side effects clearly related to the study device.
- Presence or appearance of exclusion criteria.
- Appearance of accompanying diseases rendering further participation in the study impossible.
- A significant protocol violation, as determined either by the sponsor or the investigator

- Patient noncompliant with investigational procedures
- Patient noncompliant with visits
- At the specific reasonable request of the sponsor

The sponsor must be informed in each withdrawal case. The reason for withdrawal must be recorded in the eCRF and in the patient file.

11.4 Selection of Investigators and Training

Certified gastroenterologists will be considered for participation as investigators in this study. Physicians in training (residents, fellows) and physician assistants may assist the Study Investigator in any aspect of the procedure as per standard procedures and practices at his/her institution.

Each Investigator participating in the clinical trial and the associated clinical study staff will receive training on the clinical protocol. This includes training on AE reporting, electronic Case Report Form (eCRF) completion, and Good Clinical Practice (GCP), as well as the device and system (including procedural use, device characteristics, shelf life and storage requirements, warnings, and precautions).

12.0 Study Procedures

12.1 Clinical Laboratory Investigation

Samples for hematology, serum chemistry, urinalysis will be analyzed by the local laboratory at screening, at the 2, 6 and 12 months after the EndoZip procedure.

The panels of laboratory tests to be performed are showed below:

Hematology: red blood cells (RBC) and parameters (Hemoglobin, hematocrit) and reticulocyte count, white blood cells (WBC) and differential and platelets count.

- PTT, PT and INR will be done only at the screening visit.

Comprehensive Metabolic Panel (CMP) and urine analysis :Blood glucose, HbA1c, Calcium, Albumin, Total protein, Sodium, Potassium, Total CO_2,Chloride,ALP,ALT,AST,Bilirubin.

Urinalysis: Performed locally on freshly voided clean sample by dipstick for protein, glucose, blood, pH and ketones. If the dipstick finding are abnormal based on the provided Lab values or investigator's judgment, then a microscopic evaluation will be performed to assess the abnormal findings.

Lipid screen battery including Cholesterol level, HDL, LDL and Triglycerides.

In addition, the following tests will be performed to evaluate patient health condition. Theses test will be done only at the screening and at EndoZip procedure.

Endocrinology: a quantitative β-HCG blood test (R/o Pregnancy).

12- lead electrocardiogram (ECG): The test will be performed at screening, and at EndoZip procedure day. The following will be measured or calculated: Heart rate, PR, QSR, QT, QTc and rhythm. The investigator or qualified designee will review the ECG locally and asses the results as normal or abnormal (clinically significant or not clinically significant).

12.2 Physical Examination and Vital Signs

Physical examination will include an assessment of all the major body systems.

Vital signs will include blood pressure, heart rate, pulse and body temperature and will be taken in supine position after the patient has been resting for at least 5 minutes.

Physical examination and vital signs will be taken at all in-person visits during the study. The results will be documented in the eCRF.

12.3 Body Height, Weight and Waist Circumference

Height, Weight and Waist Circumference will be measured at all in-person visits. The results will be documented in the eCRF.

Waist Circumference Measuring instructions:

To measure the waist, place a flexible tape measure between your bottom rib and your hip bone. The tape measure should be approximately in line with your belly button.

Take your waist measurement on a normal breath out

Don't pull or tuck in your stomach

Ensure the tape measure is level at the front and the back of your body

Waist Girth and Health Risk

	Men	Women
Normal	78-94cm	64-80cm
Overweight (Elevated Risk)	94-102cm	80-88cm
Obese (High Risk)	>102cm	>88cm

The tension of the tape should be such that the tape is held against the skin but not so tight as to cause an indentation in the skin

12.4 Endoscopy Procedure

Endozip™ procedure is performed with concurrent endoscopy. The procedure will be done for safety and efficacy purposes. The stitches will be evaluated with respect to the order that they were applied per stomach location and their durability. Evaluated will be done via the endoscopy performed.

Endoscopy procedure will be performed at visit 4 (2 months after the procedure) and at visit 6 (6 months after the procedure). The results will be documented in the eCRF.

12.5 Assessment of Adherence

Patients will be instructed to follow post-procedure diet and physical activities, per Appendix A. Patients will be asked to record and provide their diet and their physical activities in the provided diary log at time of their scheduled follow-up visits (Diary log is provided in appendix C). Patients adherence to the instructed regime will be assessed in all follow-up visits. Adherence to the regime will be documented in the eCRF.

12.6 Quality of Life influence and Phycological Health Questionnaire

Quality of Life influence will be evaluated via IWQOL questionnaire, filled-out by the patients at screening, and at 2, 6 and 12 months after the procedure.

Physiological health will be evaluated via PH-9 questionnaire, filled-out by the patients at screening visit and will support the patients' eligibility to the study.

The questionnaires will serve as source documents and will be transcribed into the study eCRF by Investigators or their designees.

12.7 Home Sleep Apnea Test (HSTS)

The test will be performed only for patients suffering from diagnosed obstructive sleep apnea. It will take place prior to the procedure, 2, 6 and 12 months after the procedure.

Obstructive sleep apnea (OSA) in this study is considered as a comorbidity if the hypopnea index, AHI, ≤ 15 events/hour. The purpose of the test is to evaluate if there is any improvement due to the Endozip™ procedure.

The following parameters will be measured:

1. Respiratory airflow
2. Respiratory effort
3. Oxygen saturation.

These parameters will be collected by the WatchPAT 200 (ITAMAR Medical –Israel) which is an FDA-approved portable diagnostic device that uniquely uses finger based physiology and innovative technology to enable simple and accurate Obstructive Sleep Apnea (OSA) testing.

For further instructions and guide: https://www.youtube.com/watch?v=JqZczOBcVdk

12.8 Gastric Emptying Breath Test (GEBT)

The Gastric Emptying Breath Test (GEBT), to be used with the GEBT test meal, is intended for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed

gastric emptying. The test will be performed for all patients prior to the Endozip™ procedure and 6 months after the procedure.

GEBT is a non-radioactive test that utilizes carbon-13 (13C). Labeling with 13C stable isotope is essentially safe, as 1.1% of our bodies, and of the food we eat, consists of 13C; the remaining 98.9% consists of 12C. The GEBT measures the rate of gastric emptying of solids and aids in the diagnosis of gastroparesis. The test system utilizes a gas isotope ratio mass spectrometer for the measurement of the ratio of 13CO2 to 12CO2 in breath samples. In a clinical trial comparing the GEBT and scintigraphy, the GEBT was shown to be comparable to scintigraphy. The GEBT is shown in Figure 2.

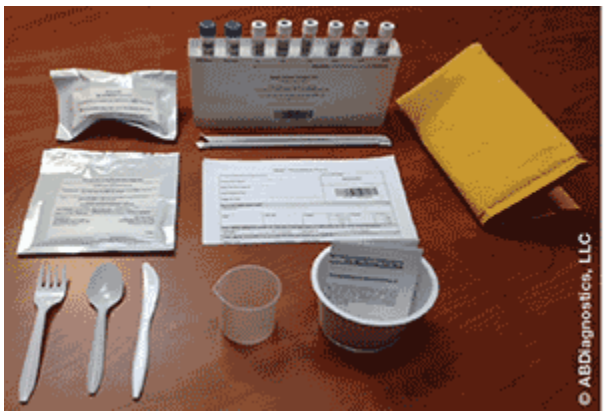


Figure 2 - GEBT kit for gastric emptying testing

Contraindications to use of the GEBT:

- Individuals with known hypersensitivity to Spirulina, egg, milk or wheat allergens should avoid the GEBT.
- Because the GEBT is an indirect multi-compartmental method of measuring gastric emptying, GEBT results may be inaccurate in individuals compromised with significant small bowel, pancreatic, liver and/or lung disease. Consequently, GEBT should not be administered to patients with pulmonary dysfunction (e.g. COPD) and/or small bowel malabsorption.

The GEBT procedure flow chart is presented in Figure 3.

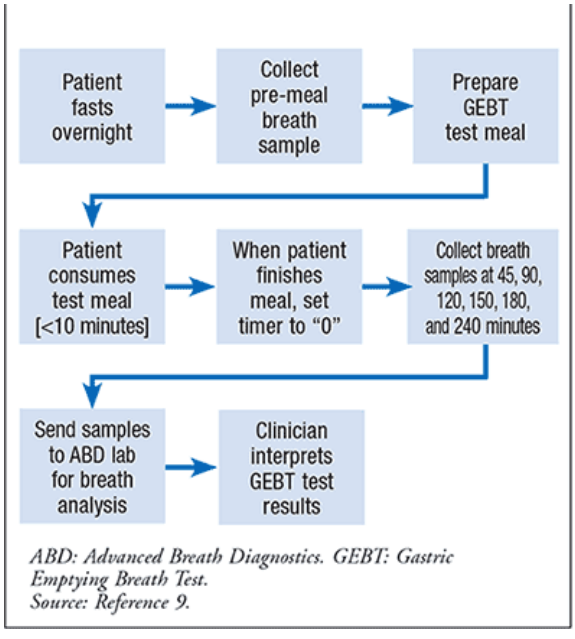


Figure 3 – GEBT Procedure Flow chart

12.1 Usability Assessment

Usability will be evaluated by a questionnaire. The physicians who will conduct the EndoZip procedure will fill-out a dedicated questionnaire specified in Appendix B. The Physician feedback will be documented in the eCRF.

13.0 Study Schedule and Activities

13.1 Visit 1 - Screening and Informed Consent

A screening/baseline will be performed prior to the scheduled EndoZip procedure to assess preoperative eligibility. The patient clinical assessment includes few tests, thus it may be done in few days.

At the screening visit, patients will be approached to obtain written informed consent prior to any study specific procedures being performed. The purpose of the study and the benefits and risks of the procedures will be explained to the patient and the consent process must be documented accordingly in the medical record. Patients who agree to study participation must sign an IEC-approved ICF. Patients will be informed that their participation in this study is voluntary and they may refuse to participate or discontinue from the study at any time. Patients will be given the opportunity to ask the investigator questions so that they are adequately informed about the research. A copy of the signed informed consent must be provided to the patient and the informed consent process will be documented in source documents.

If new information becomes available that may affect a patient's decision to continue to take part in the study, this information will be discussed with the patient by the investigator.

An identifier will be assigned to each participant signing the informed consent form. This identifier will be assigned manually, in a sequential order, in the eCRF. Numbers of patients whose participation in the study is terminated prior to procedure may not be reassigned.

All patients that are considered to have comorbidities must have definite diagnosis previously to the screening visit (by blood tests and/or imaging).

The following assessments will be performed prior to the scheduled procedure and the results recorded on the appropriate patient eCRFs: Verification of eligibility Criteria:

- Assessment of demography characteristics
- Assessment of surgical and medical history (prior abdominal surgery, GI symptoms), Obesity History
- Assessment of general medical history including use of concomitant medication

- Patient clinical condition will be assessed based on the followings:
  - Physical examination
  - Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2)
  - Waist circumference, Height, Weight
  - Laboratory evaluations (Hematology, CBC with differential, PTT, PT and INR, Comprehensive Metabolic Panel (Kidney and liver functions – blood glucose, HbA1c, Urinalysis, TSH, fasting lipid panel)
  - Gastric Emptying Breath Test (GEBT)
  - Weight on Quality of Life (IWQOL) questionnaire
  - Psychological health questionnaire-9 (PHQ-9)
  - Patients with diagnosed Sleep Apnea disorder will undergo HSAT (home sleep apnea testing).

13.1.1 Recruitment visit:

Patients who are eligible for the study will be invited to participate in the study.

Patients who were found to be not eligible for the study following signature of the Informed Consent Form will be withdrawn from the study.

13.1.2 Screen Failures

A patient is considered enrolled in the study when the ICF is signed. Only patients who receive study-assigned procedures will be followed. Patients who provide study consent, but then are determined to be ineligible will be considered screening failures and will not require additional study follow-up. The reason for the screening failure will be clearly documented, the Patient "Enrollment and Visit Log" will be completed and the patient eligibility section in visit 1 as well as a "Study Completion" form will be completed in the eCRF.

13.2 Randomization

NA –Single study arm

13.3 Visit 2 - EndoZip Procedure Day

The patients will undergo the EndoZip procedure within 30 days after signing the Informed Consent Form (ICF).

Pre-Examination Procedures:

- Verify the informed consent was obtained after explaining all risks, benefits, and alternatives to the candidate.
- Verify all Laboratory results were documented.
- Verify the GEBT results were documented.
- Verify the Quality of life (IWQOL) and Psychological health (PHQ-9) questionnaires were documented.
- For patients who suffer from Sleep Apnea, verify the Sleep Apnea test results were documented.
- Verify the patient eligibility.
- Verify all background/clinical information, demographic and medical history was documented.

In addition the patients will undergo / repeat the following test prior the EndoZip procedure:

- Physical examination
- Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) will be measured. *Note: if blood pressure measurement > 160/100 it is recommended not to perform the EndoZip procedure.*
- Weight, Height, Waist circumference will be measured.
- ECG test
- Female patients, pregnancy test
- Endoscopy screening procedure to R/O any findings in the upper GI tract.

EndoZip Procedure

The EndoZip procedure will be performed by the clinical investigator(s), experienced in endoscopic suturing devices according to local standard of care. Physicians in training (residents, fellows) and physician assistants may assist the Study Investigator in any aspect of this part of the procedure as per standard procedures and practices at his/her institution. Anesthesia will be applied as well per the standard of care. In order to ensure correct operation of the EndoZip System a NiTiNotes representative may attend the procedure. Using the EndoZip system, will followed by specific training with the device that will be provided by the sponsor prior to the study. EndoZip System operation is described in the Instruction for Use.

Once the procedure is completed, relevant data will be documented in the Electronic Case Report Form (eCRF) in addition, findings, diagnosis as well as physician's useability and satisfaction questionnaire will be recorded/completed.

The EndoZip procedure will be recorded on digital media via the endoscope equipment used during the procedure. Only the patient study ID and initials should appear in the recorded video.

All endoscopy still pictures will be saved in a digital format. Quality copies of the pictures taken during endoscopy will be provided to the sponsor.

These videos and pictures will be archived and may be used in future analyses to, for example, provide further information about observed sutures applied during the EndoZip procedure.

Any AE will be documented in the eCRF.

Post-Examination

Patients will be transferred to recovery room for observation per standard endoscopic suturing standard of care.

Standard post endoscopic suturing care is required to achieve optimal results. The study post-procedural guidance includingdiet protocol and physical activities is provided in Appendix A. Lifestyle modification will be provided by a dietitians/nutritionists.

Follow-up call will be conducted 1-2 working days after patients' discharge to verify that there has been no change in patients well-being. Any AE will be documented in the eCRF.

13.4 Visit 3 – Follow Up 1 Week Post Procedure (7-10 days after patient discharge)

The following activities will be performed and documented at this visit:

- Physical examination
- Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) will be measured
- Weight, Height, Waist circumference will be measured.
- Patients will meet with dietitians/nutritionists where he/she will be queried regarding their adherence to the post-procedure diet protocol and reminded to follow the instructions.
- Any adverse event experienced by patient since last visit will be recorded.

The relevant data will be documented in the eCRF.

13.5 Visit 4 – Follow Up 1-month Post Procedure

This visit will be conducted 1 month (±1week) after the procedure.

The following activities will be performed and documented at this visit:

- Physical examination
- Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) will be measured
- Weight, Height, Waist circumference will be measured.
- Patients will meet with dietitians/nutritionists where he/she will be queried regarding their adherence to the post-procedure diet protocol and reminded to follow the instructions.
- Concomitant medication will be recorded including any changed from the last visit.
- Any adverse event experienced by patient since last visit will be recorded.

The relevant data will be documented in the eCRF.

13.6 Visit 5 – Follow Up 2 months Post Procedure

This visit will be conducted 2 months (±1week) after the procedure.

The following activities will be performed and documented at this visit:

- Physical examination
- Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) will be measured
- Weight, Height, Waist circumference will be measured.
- Laboratory evaluations – Hematology, - CBC with differential, Comprehensive Metabolic Panel Kidney and liver functions – blood glucose, HbA1c, Urinalysis, lipid profile.
- Endoscopy procedure to inspect the stomach stitches.
- Patients will require to fill-out the IWQOL questionnaire
- Patients will meet with dietitians/nutritionists where he/she will be queried regarding their adherence to the post-procedure diet protocol and reminded to follow the instructions.
- Concomitant medication will be recorded including any changed from the last visit.
- Any adverse event experienced by patient since last visit will be recorded.
- Patients with diagnosed Sleep Apnea disorder will undergo HSAT (home sleep apnea testing).

The relevant data will be documented in the eCRF.

13.7 Visit 6 – Follow Up 6 months Post Procedure

This visit will be conducted 6 months (±1week) after the procedure.

The following activities will be performed and documented at this visit:

- Physical examination
- Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) will be measured
- Weight, Height, Waist circumference will be measured.
- Laboratory evaluations – Hematology, - CBC with differential, Comprehensive Metabolic Panel Kidney and liver functions – blood glucose, HbA1c, Urinalysis, lipid profile.
- Endoscopy procedure to inspect the stomach stitches.
- Patients will require to fill-out the IWQOL questionnaire
- Patients will meet with dietitians/nutritionists where he/she will be queried regarding their adherence to the post-procedure diet protocol and reminded to follow the instructions.
- Gastric Emptying Breath Test (GEBT)
- Concomitant medication will be recorded including any changed from the last visit.
- Any adverse event experienced by patient since last visit will be recorded.
- Patients with diagnosed Sleep Apnea disorder will undergo HSAT (home sleep apnea testing).

The relevant data will be documented in the eCRF.

13.8 Visit 7 – Follow Up 12 months Post Procedure

This visit will be conducted 12 months (±1week) after the procedure.

The following activities will be performed and documented at this visit:

- Physical examination
- Vital signs (blood pressure and heart rate - supine, pulse, body temperature, respiratory rate (RR) and SpO2) will be measured
- Weight, Height, Waist circumference will be measured.
- Laboratory evaluations – Hematology, - CBC with differential, Comprehensive Metabolic Panel Kidney and liver functions – blood glucose, HbA1c, Urinalysis, TSH, lipid profile.
- Patients with diagnosed Sleep Apnea disorder will undergo HSAT (home sleep apnea testing).
- Patients will require to fill-out the IWQOL questionnaire
- Patients will meet with dietitians/nutritionists where he/she will be queried regarding their adherence to the post-procedure diet protocol and reminded to follow the instructions.
- Concomitant medication will be recorded including any changed from the last visit.
- Any adverse event experienced by patient since last visit will be recorded.

The relevant data will be documented in the eCRF.

13.9 Additional Follow Ups

Additional Visits

Patients will receive brief (30min) telephone calls in the months that do not include in person visits (in months 3, 5, 7, 9, and 11 after the procedure). These counseling sessions are primarily designed to improve adherence to recommendations to consume a healthy diet and increase physical activity to promote weight loss and overall health.

Additional In Person Visits

In addition to the visits above, patients will visit the clinic in 4, 8 and 10 months after the procedures. In these visits, patients will meet with dietitians/nutritionists where he/she will be queried regarding their adherence to the post-procedure diet protocol and reminded to follow the instructions. These counseling sessions are primarily designed to improve adherence to recommendations to consume a healthy diet and increase physical activity to promote weight loss and overall health.

Before a patient is considered “lost to follow-up”, there must be at least three (3) documented attempts to contact the patients.

13.10 Schedule of Events

Parameters	Visit 1 Screening	Visit 2 Procedure Day (30 days after ICF)	Visit 3 1 week (7-10 days) after the discharge	Visit 4 1 month (±1wk) after the procedure	Visit 5 2 months (±1wk) after the procedure	Visit 6 6 months (±1wk) after the procedure	Visit 7 12 months (±1wk) after the procedure	Additional In-Person Vits At 4,8,10 months after the procedure
Informed consent	x							
Eligibility criteria	x							
Demographic data	x							
Medical history & concomitant medication	x		x	x	x	x	x	x
Diet & physical activity adherence		x	x	x	x	x	x	x

Parameters	Visit 1 Screening	Visit 2 Procedure Day (30 days after ICF)	Visit 3 1 week (7-10 days) after the discharge	Visit 4 1 month (±1wk) after the procedure	Visit 5 2 months (±1wk) after the procedure	Visit 6 6 months (±1wk) after the procedure	Visit 7 12 months (±1wk) after the procedure	Additional In-Person Vits At 4,8,10 months after the procedure
Weight, Height, Waist circumference	x	x	x	x	x	x	x	x
Physical examination and Vital signs	x	x	x	x	x	x	x	x
Laboratory tests	x				x	x	x	
Electrocardiogram (ECG) test		x						
Gastric Emptying Breath Test (GEBT)	x					x		

Parameters	Visit 1 Screening	Visit 2 Procedure Day (30 days after ICF)	Visit 3 1 week (7-10 days) after the discharge	Visit 4 1 month (±1wk) after the procedure	Visit 5 2 months (±1wk) after the procedure	Visit 6 6 months (±1wk) after the procedure	Visit 7 12 months (±1wk) after the procedure	Additional In-Person Vits At 4,8,10 months after the procedure
Pregnancy Test		x						
Quality of life questionnaire (IWQOL)	x				x	x	x	
Psychological health questionnaire (PHQ-9)	x							
Sleep Apnea test (HSTs)	x				x	x	x	
EndoZip™ Procedure		x						

Parameters	Visit 1 Screening	Visit 2 Procedure Day (30 days after ICF)	Visit 3 1 week (7-10 days) after the discharge	Visit 4 1 month (±1wk) after the procedure	Visit 5 2 months (±1wk) after the procedure	Visit 6 6 months (±1wk) after the procedure	Visit 7 12 months (±1wk) after the procedure	Additional In-Person Vits At 4,8,10 months after the procedure
Usability Questionnaire		x						
Endoscopy Procedure		x			x	x		
AEs and SAEs[1]		x	x	x	x	x	x	x

[1] Adverse events will be monitored continuously until the end of the study period. AEs that are still unresolved at the last study visit will be followed for outcome information until resolution or stabilization of the event for a continuous period of 2 weeks, whichever occurs first. Unresolved SAEs will be followed until resolved.

13.11 Required Concomitant Medications or Therapies

13.11.1 Concomitant Medications, Treatments, and Procedure

All concomitant prescription medications taken by the patient will be recorded as prior medications during screening and concomitant medications taken during study participation will be recorded on the electronic case report forms (eCRFs). Assessment of eligibility will include a review of permitted and prohibited medications. For details, refer to eligibility criteria.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

13.11.2 Reduce Medications, Treatments, and Procedure

Use of non-investigational medicinal products

Prophylactic topical and/or systemic antibiotic agents may be prescribed by Investigators, as rescue (or escape) medication to alleviate the anticipated adverse reactions. This may be done per recommendations in the post-procedural guidance, i.e. the post-procedural protocol used by the multidisciplinary team, or per routine local practice. NOTE: Such medication will be recorded as a concomitant medication in the appropriate study eCRF. Dose, duration and frequency will be in accordance with local practice. No special arrangements for the prescribing practices are provided in this protocol. These medicinal products do not fall within the definition of investigational medicinal products in Directive 2001/20/EC and can be referred to as NIMPs.

14.0 Statistical Analysis

14.1 Sample Size Determination

This is a pilot study that will include up to 45 patients; no statistical considerations were made to determine the sample size.

The first two (2) patients per site will be considered as run-in period, to compensate for any learning curve that may be required for the EndoZip performance evaluation.

Safety evaluation will include all enrolled patients.

14.2 Description of statistical methods

14.2.1 Analysis of Populations

Full Analysis Set (FA): includes all enrolled patients who undergone EndoZip procedure, excluding patients who enrolled in the run-in period.

Modified Full Analysis Set (mFA): The modified full (mFA) analysis set will include all patients who have at least one post initiation follow up visit and met the study Eligibility Criteria, and enrolled after the run-in period.

Per-Protocol (PP) analysis set: includes all patients from the mFA set who do not have any major protocol violations, and enrolled after the run-in period, and enrolled after the run-in period.

Statistical Analysis of Analysis Sets: Safety assessments will be performed on all enrolled patients set.

The mFA will serve as the principal data analysis set for the primary and secondary statistical efficacy endpoints. The primary, secondary efficacy assessment will also be performed on the PP and FA cohorts for descriptive purposes and to show consistency of study results.

14.2.2 General Methods:

Statistical analyses will be mainly descriptive in nature. Any statistical tests if performed will be two-sided, unless otherwise stated.
Study data will be summarized with descriptive statistics and presented in tables and figures. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum and categorical variables by a count and percentage. If multiple measurements are taken in a single patient, statistics described below will be appropriately modified to accommodate the within patient correlation.

Any deviation from specified statistical plan will be in addition to “per protocol” analysis and will be reported as such Post-hoc analysis will be conducted according to the existing data gathered, if necessary.

14.2.3 Handling of the Type I Error

The overall significance level for this study is 5%, confidence intervals will be two-sided using a 95% confidence level, except for treatment by site interaction that will be tested at a significance level of 10%.

14.3 Demographic, Medical history, and Baseline characteristics

Basic demographic and baseline characteristics will be collected during the screening visit. In addition to the evaluation of the patient's medical history in terms of study eligibility, all relevant medical conditions will be documented on the appropriate eCRF.

The patient's entire obesity history will be collected on the appropriate eCRF including previous treatments, medications and interventions done to lose weight.

Events that occur after signing of informed consent but prior to the Endozip™ procedure, unless serious and due to protocol – mandated procedure, should be recorded on the Medical History eCRF.

14.4 Primary Endpoint Analysis

The %TBWL at each visit will be calculated as 100*(Weight(BL) -Weight(Visit))/ Weight(BL), where weight is measured in kilograms. %TBWL will be summarized with descriptive statistics at each follow-up visit.

%TBWL will be evaluated by using repeated measures analysis of covariance (ANCOVA MIXED model). Baseline weight, center and visit will be used as covariates. Baseline weight will be entered as a continuous variable so that the potential for co-linearity problems will be minimized.

The unstructured covariance matrix structure will be used. If the model doesn't converge, then either the compound symmetry or autoregressive (whichever model has the lower AIC statistic) covariance matrix structure will be used instead. For this evaluation no imputation of missing data is considered beyond the model estimates.

The model estimated mean %TBWL at each visit will be presented with 95% confidence interval and level of significance.

A count and percentage of patients achieving at least 5% TBWL will be presented with exact 95% confidence interval.

14.4.1 Subset Analysis of the primary endpoint:

Additionally, the %TBWL median, mean and standard deviation and percent of patients with greater than 5%TBWL will be summarized. Covariates may include demographic data (sex, age, BMI) or other baseline characteristics.

14.5 Safety Analysis

The cumulative incidence of adverse events observed during the procedure and throughout the follow-up period, will be presented in tabular format. A detailed list of all adverse events will be presented. The

adverse event rate will be compiled with respect to seriousness, severity, expectedness and relationship to procedure and device. In addition, listings of all safety measures will be produced.

14.6 Secondary Endpoints Analysis

Excess Weight Loss % (EWL%)

EWL% of patients at 1, 2, 6 and 12 month(s) by study group will be summarized with descriptive statistics with 95% confidence intervals.

The percent excess weight loss (%EWL) will be calculated as (Weight(BL) – Weight(Visit)/ ExcessWeight(BL), where ExcessWeight(BL) is calculated as difference between the patient's baseline weight in kilograms and the kilograms at which the patient's BMI would be 25.

Change of Weight and Waist Circumference Over 12 Months from Baseline

Change from baseline in BMI at 1, 2, 6 and 12 month(s) by study group will be summarized with descriptive statistics with 95% confidence intervals.

Changes in Weight-related Quality of Life (IWQOL) Questionnaire at 12 months

IWQOL questionnaire records will be summarized by study groups will be summarized with descriptive statistics with 95% confidence intervals.

Time analysis

Time analysis including procedure duration, anesthesia duration, patient recovery duration will be evaluated and will be summarized with descriptive statistics with 95% confidence intervals.

Change in Comorbid Conditions

Clinically significant changes at 6 and 12 months in fasting plasma glucose and HbA1c concentrations, change in systolic and diastolic blood pressure, changes in plasma total cholesterol, low-density lipoprotein cholesterol and triglyceride concentrations, will be evaluated and will be summarized with descriptive statistics with 95% confidence intervals

Percentage of patients who had clinically significant change will be provided with 95% confidence interval.

Usability and Physicians' satisfaction

Physicians' satisfaction will be evaluated by a questionnaire will be summarized with descriptive statistics with 95% confidence intervals.

The physicians will be asked to fill-in a dedicated questionnaire to include their feedback on the procedure.

14.7 Interim Analyses

An interim analysis is planned after enrollment of 25 patients undergone at least 2 months of follow up aims to verify the recruitment pace and patients' adherence to the study flow.

15.0 Adverse Events (AEs) and Complications

AE and AE subcategories are defined per ISO14155:2020, as described below.

15.1 Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, user or other person, whether or not related to the investigational medical device and whether anticipated or unanticipated.

This definition includes events related to the investigational medical device or the comparator and the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

AEs will be collected starting from the time patient is enrolled until the follow-up period is completed.

15.2 Serious Adverse Event (SAE)

A Serious AE (SAE) is an AE that led to any of the following

a) Death,

b) Serious deterioration in the health of the patient, users, or other persons as defined by one or more of the following:

1) A life-threatening illness or injury, or
2) A permanent impairment of a body structure or a body function including chronic disease, or
3) In-patient or prolonged hospitalization, or
4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical

investigational plan, without serious deterioration in health, is not considered a SAE.

15.3 Serious Health Threat

Some important medical events, although they may not result in death, be life-threatening, or require hospitalization may still be considered SAEs. Life threatening means that the patient, users or other persons, was at imminent risk of death or a serious deterioration in the health, and that requires prompt remedial action, medical or surgical intervention, for other patients, users or other persons to prevent one of the outcomes listed above.
This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

15.4 Adverse Device Effect (ADE)

An Adverse Device Effect (ADE) is an AE related to the use of an investigational medical device.

This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

15.5 Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

15.6 Unanticipated Serious Adverse Device Effect (USADE)

An Unanticipated Serious Adverse Device Effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

15.7 Adverse Event Severity Classification

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with activities of daily living (ADL); Minimal local or noninvasive intervention indicated.

Severe	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL*

Severity will be defined according to the following criteria:

NOTE: An AE can be classified as severe and not deemed a SAE. Similarly, a SAE is not automatically severe in nature.

* Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

15.8 Adverse Event Relationship Classification

Relationship to study product administration will be determined as follows:

- *No Relationship*: No relationship between the AE and the administration of study treatment and a known relationship to other etiologies such as concomitant medications, procedure, or patient's clinical state.
- *Possible Relationship:* An AE that follows a reasonable temporal sequence from administration of the study treatment and follows a known response pattern to the study treatment but could have been produced by the participant's clinical state or by other therapies.
- *Probable Relationship:* An AE that follows a reasonable temporal sequence from administration of the study treatment; follows a known response pattern to the study treatment; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.
- *Definite Relationship:* An AE that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the study treatment. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
- *Unknown/Impossible to Determine:* Given the information available, sequence and timing of events, it is unknown or impossible to determine the relationship of the AE with the study treatment.

15.9 Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

- *Resolved:* The event has fully resolved at the end of the study.

- *Resolved with sequelae*: The event has resolved, but retained pathological conditions resulting from the prior disease or injury.
- *Continuing:* The event is ongoing at the end of the study.
- *Death:* This event is determined to be the cause of death.

15.10 Device Deficiencies

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or use error and inadequate labeling.

All device deficiencies will be documented, and the device should be returned to NiTiNotes for analysis, if possible. Instructions for returning the investigational device will be provided. Device deficiencies should also be documented in the patient's medical record.

Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

15.11 Adverse Event Recording and Reporting

Assessment of the occurrence of an AE will be based on changes in the patient's signs and symptoms. AEs will be monitored until a patient completes the study unless the Investigator determines the event is related to the investigational device, in which case they will be monitored until resolution if possible. Medical care will be provided, as defined in the informed consent, for any AE related to study participation. AEs will be collected on an AE eCRF and applicable source documentation.

The following should not be considered an AE:

- A condition requiring a preplanned procedure unless the condition worsened since screening
- A preexisting condition found as a result of screening, unless the condition has worsened since enrollment.

All AEs observed during the course of this study, regardless of severity or relationship to the investigational device will be recorded on the appropriate eCRF.

15.11.1 Data Safety and Monitoring Board (DSMB)

An independent group of experts chosen by the sponsor will constitute the Data and Safety Monitoring Board (DSMB). The DSMB will review and adjudicate all serious device related and non-related adverse events and any other events deemed necessary. The Adverse Events will be reported

as per the standard clinical practices. All adverse event incidence rates will be summarized by anticipation, severity and relationship to the investigational device.

The incidence of major complications using the EndoZip system will be presented.

15.12 Reporting Responsibilities

Throughout the course of the study, all efforts will be made to capture and evaluate adverse events. If an adverse event occurs, the first concern is for the safety and welfare of the patient. Appropriate medical intervention will be made. All adverse events observed by the Investigator or reported by the patient, whether or not related to the EndoZip system or to a study-procedure, have to be recorded in the appropriate section of the patient's eCRF. eCRFs will be captured and monitored throughout the study. Information about AEs will include as a minimum the description of the event, date of onset, date the event was noticed by Investigator, an evaluation of the relatedness of the adverse event to the EndoZip system and /or study procedure, medical assessment for seriousness, actions taken and whether study participation was discontinued.

A pre-existing condition, which is a condition that is present at the beginning of the study, should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

All Adverse Events still on-going at the end of the study period need to be followed until resolution.

Serious Adverse Events will be reported by the Investigator to the sponsor with no delay, and no later than 2 days after the Investigator learned about the event. The Investigator will use the study specific eCRF reporting form. SAEs will be processed and reported by Sponsor to Competent Authorities and Ethics Committees according to the applicable local regulations. Serious adverse events that are still on-going at the end of the study period must be followed up to determine the final outcome.

The investigator is responsible for the classification of adverse events and together with the sponsor for the ongoing safety evaluation of the clinical investigation. The sponsor shall:

- Forward all AE records and the investigator's assessment to the DSMB. The DSMB will fulfill its responsibility to monitor the safety of patients by conducting formal reviews of the accumulated safety data. These reviews will normally occur at regular intervals, however, in case of specific concerns, ad-hoc meetings can be set up.

  A DSMB will evaluate the AE for their relatedness to the investigational device and will make recommendation regarding reporting, continuation, modification, or termination of the trial. The

DSMB will determine and document in writing their seriousness and relationship to the investigational device.

- Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect;

- Report or ensure the reporting, to the IEC by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or by the IEC . The investigator must inform the sponsor and the local IEC about any serious adverse effects and serious adverse device effects as soon as becoming aware of the occurrence by Fax/Telephone.

- Report to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations

- Inform all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that they are reported to their IEC , if required by national regulations; this information shall be sent to all the principal investigators within a time frame established based on the perceived risk as defined in the risk analysis report

- Ensure that the IEC and the regulatory authorities are informed of significant new information about the clinical investigation.

- In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

16.0 Ethics and Compliance

16.1 Statement of Compliance

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155:2020 (Clinical Investigation of Medical Devices for Human Patients – Good Clinical Practice), ICH-GCP, and any regional or national regulations, as appropriate.

This may include an inspection by NiTiNotes representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/ NiTiNotes representatives and must allow direct access to source documents to the Regulatory Authority/ NiTiNotes representatives. Regulatory Authority

approvals/authorizations/notifications, where required, will also be in place and fully documented prior to study start.

16.2 Protocol Compliance

No changes to the protocol will be permitted without the written approval from NiTiNotes and the IEC. The investigator must notify NiTiNotes and the reviewing IEC of any deviation from the Investigational Plan when specific to the protection of the life or physical well-being of a patient in an emergency. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency has occurred. Except in such an emergency, prior written approval by NiTiNotes is required for changes in or deviations from the Plan. If these changes or deviations affect the scientific soundness of the Plan or the rights, safety, or welfare of human patients the IEC will also be notified. All other deviations will be reported per the site's IEC deviation policy. Should any deviations from the Investigational Plan occur, these will be reviewed by NiTiNotes for their clinical significance. If the event is performed without written approval from all parties, the investigator may be terminated from the study.

16.3 Institutional Review Board/Institutional Ethics Committee (IRB/IEC)

Documented approval from the appropriate Institutional Review Board /Ethics Committee (IRB/IEC) will be obtained for all participating centers prior to study start, according to ICH GCP, local laws, regulations, and organization. When necessary, an extension, amendment, or renewal of the IEC approval must be obtained. The IEC must supply to the sponsor a list of the IRB/IEC membership and a statement to confirm that the IEC is organized and operates according to GCP and applicable laws and regulations.

16.4 Patient Informed Consent

A core information and consent form will be provided. Prior to the beginning of the trial, the investigator must have the IEC written approval/favorable opinion of the written ICF and any other written information to be provided to patients. The written approval of the IEC together with the approved patient information/ICFs must be filed in the study files.

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s), and must adhere to GCP and to the ethical principles originating in the Declaration of Helsinki. Written informed consent must be obtained before any study specific procedure takes place. Participation in the trial and date of informed consent given by the patient should be documented appropriately in the patient files.

16.5 Insurance

All patients participating in the trial will have insurance coverage by the Sponsor, which is in line with applicable local laws.

16.6 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will be kept confidential. Only the patient number and initials will be recorded in the eCRF, and if the patient name appears on any other document, it must be obliterated. In cases were the local low does not allow using the patient initials serial number will be appointed (e.g. AAA, BBB). Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, IEC or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. Patients will also be informed that information regarding the study that does not include patient identifiers will be posted on clinicaltrials.gov.

If the results of the trial are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients' records to be identified.

16.7 Use of Data and Publications

Information regarding the study and study data will be made available via publication on clintrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of NiTiNotes, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators, educational, further product development and marketing uses.

The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor 45 days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

Disclosure of involvement in a publication (e.g., sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be as specified by journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by International Committee of Medical Journal Editors. Authors must ensure that an acknowledgement/disclosure statement is included in the body of the manuscript for NiTiNotes to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal requirements.

17.0 Monitoring Procedures

Site visits will be conducted by an authorized NiTiNotes representative to inspect study data, patients' medical records, and eCRFs in accordance with current ICH GCPs and the respective local and national government regulations and guidelines (if applicable).The Study Investigator and the investigating site will permit authorized clinical research personnel and clinical monitors from NiTiNotes and/or designee(s) employed by NiTiNotes to review completed eCRFs, IEC decisions, and Investigator, clinical site records, and facilities relevant to this study at regular intervals throughout the study per the monitoring plan. Additionally, patient charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. The accuracy and quality of the data obtained from the investigator and maintained by NiTiNotes will be confirmed through a structured program of clinical field auditing and internal review detailed in the monitoring plan. In instances where data protection regulations prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor. Monitoring may be performed with in person visits or remotely, when applicable.

To ensure the rights, safety, and welfare of study patients are being maintained, the monitor will review training records to ensure all study staff are trained on the study protocol and use of the study devices. If the monitor discovers that an investigator is not complying with the signed Investigator Agreement, the investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IEC, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, device shipments to the investigator may be discontinued and the investigator's participation in the investigation terminated. The monitor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a patient.

17.1 Data Collection and Processing

This study will utilize an (electronic Case Report Form) eCRFs. All data requested on the eCRFs are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified.

The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her signature on the appropriate eCRFs and will be documented in compliance with local regulations. In accordance with current ICH GCPs and the respective local and national government regulations and guidelines, audit trail shall be used to capture any changes to data previously entered to the eCRF, including when changes where made, by whom and the reason for the changes.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created and will be issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database.

18.0 Study Supplies and Device Accountability

18.1 Packaging

The EndoZip disposables are composed of biocompatible parts and are supplied sterile in a sealed package.

18.2 Labeling

All packages are labeled in conformance to NiTiNotes Packaging Best Practice. Study devices will be labeled as “For Investigation Use Only”.

18.3 Inventory Control

The sponsor will initiate shipment of the product from the sponsor to the site upon receiving all required documents (e.g., approval/favorable opinion from IEC). The sponsor will maintain tracking for all shipment documentation. Prior to any shipment, the site will be informed by the sponsor of the upcoming shipment, expected arrival date, and content of the shipment. The site should confirm receipt of the shipment.

An Investigator’s Device Accountability form will be conducted under the Regulatory Binder at each site.

In case of technical failure, the site will approach the NiTiNotes representative which will help solve the problem.

For each dispensed EndoZip, the following information should be recorded:

- The patient study number
- Date dispensed
- Device ID number

At the termination of the study, all unused study material must be returned with the corresponding documentation as directed by NiTiNotes.

18.4 Retention of Records

All source documents and eCRFs will be kept for a period of no less than five years after the later of the following dates: the date of which the study is terminated or completed or; the date that the records are no longer required supporting marketing applications.

18.5 Study Completion/Termination of Study

NiTiNotes reserves the right to discontinue the study at any stage, with suitable written notice to all investigators and reviewing IECs, following unforeseen events or other factors that do not permit continuation of the study. Similarly, investigators may withdraw from the study at any time, patient to providing written notification to NiTiNotes 30 days prior to the date they intend to withdraw. However, NiTiNotes and investigators will be bound by their obligation to complete the follow-up of patients already participating in the study. The patients must be followed according to the clinical protocol, and information obtained during patient follow-up shall be reported to NiTiNotes on the appropriate eCRF.

The appropriate ethics committees will be notified of discontinuation of the trial for any reason not later than 15 working days after the sponsor makes this determination and not later than 30 days after the sponsor receives a notice from the ethics committee and/or regulatory authority.

19.0 General Information

19.1 Study Contact Information

Questions should be directed to Clinical Affairs.

Clinical Affairs
Hagit Ephrath VP of QA, Regulatory and Clinical Affairs NiTiNotes Ltd. Address: 5Haeshel st, PO box 3158, Caesarea, Israel Tel: +972-4-8876698 Fax: +972-4- 8864358 Mobile: +972 (52) 314-2045 Email: hagit@nitinotesurgical.com

19.2 Use of Data and Publications

Information regarding the study and study data will be made available via publication on clintrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of NiTiNotes, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators, educational, further product development and marketing uses.

The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor 45 days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

Disclosure of involvement in a publication (e.g., sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be as specified by journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by International Committee of Medical Journal Editors. Authors must ensure that an acknowledgement/disclosure statement is included in the body of the manuscript for NiTiNotes to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal requirements.

20.0 REFERENCES

1. World Health Organization (WHO) Obesity and overweight Fact sheet Updated June 2016

2. Legal KM, Carroll MD, Ogdan CL, Curtin LR, Prevalence and trends in obesity among US adults 1999-2008 JAMA, 2010 Jan 20 303 (3) 235-41.

3. Centres for Disease Control (CDC)

4. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient: 2013 update—cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. Surg Obes Relat Dis 2013; 9:159–191.

21.0 Appendix A: Post Procedure Regime

21.1 Pre-Procedure diet

- Patients will follow a clear liquid diet starting 24 hours prior to scheduled arrival time for the procedure
- Patients will be NPO after midnight the night before the procedure. (exception - small sips of water for medication)

21.2 Post Procedure Diet

At each individual session, dietitians will perform a diet recall and exercise recall to determine compliance with the diet recommendations and the exercise goals. The dietitian will discuss the barriers patients have that may be preventing them from achieving their diet recommendations and their exercise goals. In conjunction with the patient, the dietitian will set 1-3 goals for the patients to work on before the next session.

The patient will be under the following diet regime from Day 0 to Week 8 Post Procedure (PP, Table 1)

Table 1. Diet Progression

Phase	Duration	Types of Liquids or Foods	Protein Goal	Notes
Phase 1: Clear liquid diet	PP Day 1 to PP Day 3	Clear Liquids only	60-80 gm	• Will need protein supplement to maintain protein goals • Focus on protein intake, adherence to clears, and sufficient liquids to avoid dehydration total calories may be low
Phase 2: Full liquid diet	PP Day 4-PP Day 14	Full Liquids and Clear Liquid	60-80 gm	• Will need protein supplements to maintain protein goals • Still need to focus more on protein intake and sufficient liquids to avoid dehydration • Total calories may be low, but if patient can maintain activities, hydration, and energy level do not force additional intake

Phase	Duration	Types of Liquids or Foods	Protein Goal	Notes
Phase 3: Semi-Liquid (Pureed) Diet	PP Day 15 to PP Day 42	Pureed Food, Full Liquids, and Clear Liquids	60-100gm (higher protein range for tall patients and men)	• May still need protein supplements • Eat pureed meals slowly – discomfort can occur quickly Avoid fluid intake within 30 min of a meal
Phase 4: Semi-Solid Diet	PP Week 6-PP Week 8	Add soft foods that can be easily chewed	60-100 gm (higher protein range for taller patients and men)	• Still continue to eat slowly and chew food well • Continue to drink between meals and stop 30 min before a meal
Phase 5: 1200 – 1500 Calories Diet				

21.3 Phase 1: Clear Liquids Only

Water-based diet for 2-3 days after the procedure.

Recommendation for Patients:

- You can start Clear Liquids when awake after the procedure.
- Clear liquids are liquids that you are able to see through when you hold up a glass of the liquid to light. Examples include sugar-free and room temperature water, light tea, chamomile, herbal teas, and Jelly.
- They are easily digested and leave no undigested residue in your intestinal tract.
- Medium temperature or room temperature liquids may be better tolerated than extremely cold and extremely hot liquids after the procedure.
- For adequate protein on a clear liquid diet, you NEED to supplement.
- Aim for 60g of protein per day and 48 fluid ounces per day. You can purchase protein powder online
- Consume 2 tablespoons/30 cc of clear liquids every 15 minutes in order to maintain hydration.
- Use a timer to accurately track 15 minutes and avoid dehydration.
- Avoid caffeine and alcohol for 1 month, as these can cause stomach irritation and dehydration as you heal.
- Avoid sugary drinks, which can lead to diarrhea.
- Avoid carbonated beverages for 1 month, along with using straws, as this can lead to the swallowing of more air.
- Do not gulp liquids – be sure to sip.
- Avoid chewing gum to prevent taking in more air as well.

21.4 Phase 2: Full Liquid Diet

Recommendation for Patients:

- All liquids should pour off a spoon.
- Consume foods that are liquid or semi-liquid at room temperature.
- You may not feel hungry most of the time and find it difficult to eat even three times a day.
- Small portions sizes are essential!
- Eat your meals slowly. Allow for 20-30 minutes per meal.
- Drink water or zero-calorie fluids throughout the day.
    - Your goal is 1.5 liters of fluids a day, working up to 2 liters of fluids a day.
    - Drink between meals but not right before or during.
    - NO straws. You can suck up too much air and cause discomfort.
    - Sip, sip, sip.

Recommended Foods:

- Any of the food from Stage 1-Clear Liquids
- Milk or milk alternatives (low-fat or non-fat is preferred).
- Creamed soups
- Broth based soups run through the blender, no lumps or bumps
- Protein supplement drinks
    - With at least 15g protein and less than 3g of sugar.
    - Popular brand: Unjury Protein or Premier Protein
- Thinned hot cereal:
    - Cream of wheat
    - Instant oatmeal
- Thinned mashed potatoes (thinned with chicken, vegetable, or beef broth)
    - Flavoring ideas:
        - Thyme, oregano, basil, garlic, onion powder
        - Packaged gravy mix
- Low-sugar yogurt or sugar-free pudding
- Low-sugar light, drinkable yogurt

Between Meal Liquids: (low calorie, less than 10 Calories per 8 fluid ounces)

- Water
- Sugar-free flavored drink packets
- Broth
- Decaffeinated coffee or tea – fat free creamer and sugar substitute are OK
- Tomato or vegetable juice (limit to 6 fluid ounces per day)

Sample Meal Plan:

Between meals liquids (low calories, less than 10 calories per 220 cc liquids – 1 cup)

- Water
- Sugar-free flavored drink packets
- Decaffeinated coffee or tea – fat free creamer and sugar substitute are OK
- Tomato or vegetable juice (limit to 175 cc fluids per day)

Breakfast – 120ml of Semolina / rice cream

Snack – 120ml of 1% milk with a spoon of protein powder / other protein drink

Lunch – 120ml creamed soup

Snack – 120ml of 1% milk with a spoon of protein powder / other protein drink

Dinner – 120ml filtered chicken soup

Snack – 120ml of 1% milk with a spoon of protein powder / other protein drink

21.5 Phase 3: Semi-Liquid (Pureed) Diet

Recommendation for Patients:

This diet includes:

- Foods that do not need much chewing.
- Typically, ground, pressed, blended, or sieved to the consistency of a soft creamy paste or thick liquid.
- Continue drinking fluid between your meals, but stop 30 minutes before your meal and start again 60 minutes after your meal.

Recommended Foods:

- All foods from the clear liquid and full liquid diets
- Low-sugar yogurt
- Low-fat white cheese
- Scrambled eggs
- Pureed beef, chicken, or turkey
- White fish mashed finely with a fork
- Tuna mashed finely with a fork
- Mashed or pureed potatoes/sweet potatoes
- Pureed cooked butternut squash

- Pureed cooked spinach, carrots, green beans
- Tahani
- Avocado
- Banana

Sample Meal Plan:

Snacks (mid morning and mid afternoon)

- 120 ml skimmed milk
- 125 g low fat white yogurt / cheese
- 1 teaspoon almond butter
- I teaspoon of natural peanut butter
- 1 spoon of tahini

Breakfast – 1 scrambled egg + 0.5 cup of low fat white cheese + decaffeinated coffee/tea

Snack – 130g Fruit puree

Lunch – 100-150 g Pureed beef, chicken, or turkey + 100 ml vegetable puree (chard, spinach, lettuce, zucchini, broccoli)

Snack – 125 g low fat white yogurt

Dinner – 120ml filtered chicken soup

Snack – 120ml of 1% milk with a spoon of protein powder / other protein drink

21.6 Phase 4: Semi-Solid Diet

Table 2. Phase 4 and 5: Protein goals and Maximum calorie amounts

Start Weight	68-89		90-112		113 and above	
Calories or Protein	kcal	protein	kcal	protein	kcal	protein
Amount	1200	60-80	1300	70-90	1500	80-100

Both calories and protein need to be tailored to the patient. The calories listed are the maximum goals – patients should not eat over this amount, but can eat less. Many patients will eat less than these calorie levels in the first few months after the procedure.

If patients are eating less than the amounts listed below, have no evidence of dehydration and

have good energy levels they do not need to force additional calorie intake. **Forcing food/volume can lead to patient discomfort / adverse events and should be avoided.**

Recommendation for Patients:

This diet includes:

- Foods that are easily chewed and swallowed.
- Avoid foods that are hard like nuts, popcorn, or seeds, stringy like cooked onions and cooked bell peppers, or tough like dried fruit or smoked meats.
- Avoid foods that can cause gas like broccoli, Brussel sprouts, cabbage, cauliflower, bell peppers and onions.
- Vegetables should still be cooked in this phase and all food should be chewed thoroughly.

Recommended Foods:

- Anything in the prior diet phases
- Moist and tender meats
- Cooked or canned fruits
- Banana
- Avocado
- Tahini
- Cooked vegetables
- Plain, white rice, pasta-no more than 1/3 of a cup
- Refined wheat bread
- Homemade hummus

Snacks (mid morning and mid afternoon)

- 120 ml skimmed milk
- 125 g low fat white yogurt / cheese
- 25g light Emmental cheese
- 1 teaspoon almond butter
- I teaspoon of natural peanut butter
- 1 spoon of tahini / avocado spread
- 3 spoons smooth homemade hummus
- 130g Fruit puree

Sample Meal Plan:

Breakfast – 1 scrambled egg + 25g light Emmental cheese + decaffeinated coffee/tea

Snack – 130g Fruit puree

Lunch – 160 g fish pureed or well chopped + Ricotta 70 g / Philadelphia light 60g + 110 g mashed or pureed potatoes/sweet potatoes

Snack – 120ml of 1% milk with a spoon of protein powder / other protein drink

Dinner –20 g Semolina / rice cream / small pasta in 100ml vegetable broth + 5 g parmesan cheese

21.7 Phase 5: 1200 – 1500 Calories Diet

Recommendation for Patients:

This diet includes:

- 1,200-1,500 kcal/day diet
- 60-80g of protein/day (20g of protein at breakfast)
- Eat small amounts, several times a day.
- Set utensils down in-between bites.
- Eat slowly, and stop at first sign of fullness.
- Chew foods thoroughly.
- Drink non-caloric beverages, avoid drinking gassy beverages, and drink in-between meals.

The following menu is designed according to the following calorie distribution:

- Breakfast – 200 -300 calories
- Snacks - 100 calories
- Lunch – 500 - 600 calories
- Snacks - 100 calories
- Evening – 300 - 400 calories

Sample Meal Plan:

Breakfast:

1 cup of low fat white yogurt (you can use yogurt enriched with protein 20 grams of natural protein) + half a cup of freshly cut fruit, 5 almonds / nuts

OR

2 slices of light bread made from rye / spelled / 3 slices of cracker made from rice / buckwheat / corn (each up to 30 calories) / a half pita beard made from whole wheat / spelled + 1 spoon of white cheese 5% + hard-boiled egg + slices of vegetable (tomato / cucumber / red pepper) and leaf . lettuce
OR
3 spoons oatmeal + 0.5 cup of skimmed milk / herbal drink + 0.5 cup of water + chopped fresh banana and a little cinnamon

Snacks:
1.5 cup melon / watermelon cubes or other fresh fruit (1 medium unit)
OR
2 spoons white cheese 5% with fresh vegetables (5 cherry tomatoes, cucumber + 0.5 carrot)

Noon:
150 g baked salmon (can be used with herbs and lemon) / chicken breast + 3 spoons whole rice / quinoa / medium sweet potato + a cup of green beans in tomato sauce / a small bowl of (volume of a cup) vegetable salad with 1 teaspoon of olive oil / 1 spoon avocado
OR
120 grams of tofu cubes + 0.5 cup of cooked rice noodles or quinoa noodles + 2 cups of stir-fried vegetables (such as carrots, celery, mushrooms, onions, cabbage, cauliflower, broccoli ...) - for the sauce - 2 spoons soy sauce and 1 spoon of olive oil
Snacks:
Energy snack up to 100 calories / 1 date palms or 1 fresh fruit + 4 walnut or almond halves / Ice cream up to 100 calories / 2 crackers (up to 30 calories per unit) + a teaspoon of jam / honey on each cracker

Evening:
Omelet (1 egg) with herbs (onion, parsley, rocket, spinach) + 2 spoons cheese / white cheese 5% with vegetable salad + quarter avocado + 2 slices light bread / 1 slice of bread made from whole wheat / spelled / rye
OR
Tuna salad: 50 grams (one third of a box) tuna in water + hard-boiled egg + vegetable salad with a seasoning of 1 teaspoon of olive oil, half pita bread from spelled / whole wheat (up to 100 calories per pita)
OR

1 cup of low fat white yogurt (you can enriched with natural-flavored protein) + whole apple + half pear + half nectarine + 2 flat spoons of granola without added sugar + 1 teaspoon of chia seeds

21.8 General Instructions

The information supplements the diet plan (divided into progressive phases) described above.
They have been inserted to help operated patients to change their eating habits in order to reduce complications and side effects after the EndoZip procedure.

- **The re-feeding phase duration (respecting the indicated times)** will be strictly related to individual tolerance. If the introduction of new foods or foods with a different consistency might determine excessive gastric filling or vomiting, please return to previous PHASE diet for 2-3 days.
- **Eat slowly**, chewing your food well and stopping between one bite and the next. The meal must last at least 30-40 minutes.
- **Stop eating as soon as you feel full** (regardless of the amount of food ingested). Insisting would cause vomiting.
- Start lunch and dinner with the protein dish to ensure adequate protein intake during weight loss; then continue the meal with vegetables, fruit and finally the first course.
- Avoid eating and drinking at the same time.
- Do not induce vomiting.
- Eat the evening meal at least 2 hours before bedtime, to avoid the onset of gastroesophageal reflux.
- Drinks should be taken at least half an hour after the meal (before or after).
- Drink, initially, at least 1 liter of water during the day, only natural, in small sips. Tea, chamomile, barley, preferably decaffeinated coffee, herbal teas as long as they are sugar-free or using natural sweeteners based on Stevia are also allowed.
- **Avoid the consumption of carbonated, sugary, alcoholic and spirits drinks.**
- Vegetables should not be eaten in the first few weeks; they will then be reinserted gradually and in small quantities in the form of pureed vegetables or finely chopped.
- **Avoid the consumption of foods containing simple sugars and fats** (sweets, jams, honey, croissant, chocolate, ice cream, dried and canned fruit, fruit juices, spicy cheeses, sausages, sauces and various condiments).
- Avoid foods that are too spicy, too hot or too cold.
- In the final phase, divide up the meals of the day respecting the times (3 main meals + 1 mid-morning and mid-afternoon snack). Any changes must be agreed with the doctor.

- In case of constipation make sure to introduce an adequate supply of water. However, it is possible that the doctor will recommend taking laxatives.
- Gradually increase physical activity (after consulting your doctor and based on your physical condition), so as to preserve muscle mass in conjunction with weight loss.

21.9 Physical Activity

For patients who exercised regularly (defined as at least 3 days per week for at least 30 minutes per session) before the procedure can return to exercise as tolerated once they are at least on a full liquid diet and have no post-procedure symptoms. For patients who have never exercised before, consider the following exercise titration in Table 2 after the patient has advanced to a pureed diet and their post-procedure symptoms have resolved.

1. The recommended exercise is at least moderate intensity exercise (brisk walk). High intensity training and high intensity interval training are also acceptable. Strength training is also encouraged
2. Goals: after return to exercise or titration of exercise 150 minutes of at least moderate intensity exercise (e.g. brisk walk with moderate breathing) per week

Table 2. Exercise progression

Week Post procedure	Moderate Intensity Exercise Duration	Sessions Per Week
2 Weeks PP	15 minutes	3
3 Weeks PP	15 min	4
4 Weeks PP	20 min	4
5 Weeks PP	20 min	5
6 weeks PP	30 min	5

22.0 Appendix B – Usability Questionnaire (filled-in by the physician)

1. How was it to remove the system from the pack maintaining its sterility?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

2. How was the system setting up with respect to the followings?

   a. Connect to the electricity

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

   b. Connect to the vacuum pump system

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

   c. Connect to the Endoscope system

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

   d. Connect to the CO_2 system (if used)

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

☐ N/A (if CO_2 not been used during the procedure)

3. How was the insertion of the scope into the EndoZip device?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

4. How was the system advancement to the stomach through the Overtube?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

5. How was the maneuvering process within the stomach to the desired suturing location?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

6. For insufflation, did you use the EndoZip CO_2 channel? ☐ Yes ☐ No

   a. If No, how was the insufflation process using the endoscope insufflation channel?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

   b. If Yes, how was the insufflation process using the endoscope and the EndoZip CO2 extra channel?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

7. How was the overall management of the system's stopcocks, clamps and valves (vacuum and CO_2 insufflation)?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

8. How was the overall management of the system's knobs (for proximal and distal articulation)?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

9. How easy was the activation of operation button? (suturing, tightening, clipping and cutting process)

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

10. How easy was the identification of suturing stage through the system user panel (LEDs)?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

11. How was the Corset wire release process (before system retrieval)?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

12. How was the system retrieval process?

Very Easy	Easy	Acceptable	Difficult	Very Difficult
5	4	3	2	1

General impression:

1. How was the general touch and feel working with the EndoZip system?

Excellent	Good	Acceptable	Difficult	Unacceptable
5	4	3	2	1

2. How was the use of Endozip system, comparing to ESG alternatives?

Significantly Easier	Easier	Same	Inferior	Significantly Inferior
5	4	3	2	1

Please grade your agreement with the following statements:

3. I think that I would like to use this system frequently

Strongly Agree				Strongly Disagree
5	4	3	2	1

4. I thought the system was easy to use

Strongly Agree				Strongly Disagree
5	4	3	2	1

5. I think that I would need the support of a technical person to be able to use this system

Strongly Agree				Strongly Disagree
5	4	3	2	1

6. I found the various functions in this system were well integrated

Strongly Agree				Strongly Disagree
5	4	3	2	1

7. I found the IFU (Instruction For Use) very informative and provides sufficiently the information needed to perform the procedure

Strongly Agree				Strongly Disagree
5	4	3	2	1

Comments_____

_____

_____

_____

23.0 Appendix C – Patients Diary (filled-in by the patients)

Date: ___ / ___ / 2021
dd mm

Breakfast	_____ _____ _____ _____
Snack	_____ _____
Lunch	_____ _____ _____ _____
Snack	_____ _____
Dinner	_____ _____ _____ _____