DE NOVO CLASSIFICATION REQUEST FOR APOLLO ESG, APOLLO ESG SX, APOLLO REVISE, APOLLO REVISE SX SYSTEMS

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Endoscopic suturing device for altering gastric anatomy for weight loss.** An endoscopic suturing device for altering gastric anatomy for weight loss uses suturing to approximate gastric tissue to restrict the volume of the stomach for the intended purpose of weight loss.

NEW REGULATION NUMBER: 21 CFR 876.5983

CLASSIFICATION: Class II

PRODUCT CODE: QTD

BACKGROUND

DEVICE NAME: APOLLO ESG, APOLLO ESG SX, APOLLO REVISE, APOLLO REVISE SX Systems

SUBMISSION NUMBER: DEN210045

DATE DE NOVO RECEIVED: September 30, 2021

SPONSOR INFORMATION:

Apollo Endosurgery, Inc.
1120 S. Capital of Texas Hwy., Bldg. 1, Ste 300
Austin, TX 78746

INDICATIONS FOR USE

The APOLLO ESG and ESG SX Systems are intended to be used by trained gastroenterologists or surgeons that perform bariatric procedures to facilitate weight loss by reducing stomach volume through endoscopic sleeve gastroplasty in adult patients with obesity with BMI 30 -50 kg/m^2 who have not been able to lose weight, or maintain weight loss, through more conservative measures.

The APOLLO REVISE and REVISE SX Systems are intended to be used by trained gastroenterologists or surgeons that perform bariatric procedures to facilitate weight loss in adult patients with obesity with BMI 30 - 50 kg/m^2 by enabling transoral outlet reduction as a revision to a previous bariatric procedure.

LIMITATIONS

The sale, distribution, and use of APOLLO ESG, ESG SX, REVISE and REVISE SX Systems are restricted to prescription use in accordance with 21 CFR 801.109.

In the clinical study of the device, patients were required to supplement device use with a low-calorie, healthy lifestyle intervention program.

APOLLO ESG, ESG SX, REVISE and REVISE SX Systems should only be used by gastroenterologists and surgeons who have undergone specific training by the device manufacturer.

APOLLO ESG, ESG SX, REVISE and REVISE SX Systems are contraindicated for use under the following conditions:

- This system is not for use where endoscopic interventions are contraindicated.
- This system is not for use on malignant tissue.
- Large hiatal hernia.
- Potential bleeding gastric lesions (e.g. ulcers; erosive gastritis; varices; or vascular malformations).
- Affective disorders not under medical supervision or refractory to medical therapy and all eating disorders (e.g. anorexia nervosa; binge eating disorder; specified feeding and eating disorders; avoidant restrictive food intake; rumination).
- Women who are pregnant.
- Coagulopathy and antiplatelet/anticoagulant therapy that cannot be corrected.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

Endoscopic Sleeve Gastroplasty (ESG) is an endoscopic procedure that involves the creation of plications in the stomach to reduce stomach volume. The plications form a sleeve, which reduces stomach capacity and slows gastric emptying.

Patients having previous Roux-en-Y gastric bypass bariatric surgery may experience dilation of the gastrojejunostomy outlet and the gastric pouch, followed by weight gain. This can be addressed by reducing the diameter of the gastric outlet by suturing. This procedure is often referred to as Transoral Outlet Reduction (TORe).

The APOLLO ESG and APOLLO REVISE Systems are designed to accomplish ESG and TORe, respectively, using a dual channel scope. The APOLLO ESG and APOLLO REVISE System components and the respective quantities are shown in Table 1 below.

Table 1: Components and quantities for APOLLO ESG and APOLLO REVISE Systems

Component	APOLLO ESG	APOLLO REVISE
OverStitch Handle (ESS-G02-160) to perform suture manipulations.	1	1
Tissue Helix (THX-165-028) to bring tissue into the suturing window.	1	1
Suture-anchors (PLY-G02-020-APL or PLY-G02-020-A, depending on geography) to affect plications.	8	6
Cinch devices (CNH-G01-000) to lock the sutures in place.	8	6

The APOLLO ESG SX and APOLLO REVISE SX Systems are designed to accomplish ESG and TORe, respectively, using a single channel endoscope. The APOLLO ESG SX and APOLLO REVISE SX System components and the respective quantities are shown in Table 2 below.

Table 2: Component and quantities for APOLLO ESG SX and APOLLO REVISE SX Systems

Component	APOLLO ESG SX	APOLLO REVISE SX
OverStitch SX Handle (ESS-G02-Sx1) to perform suture manipulations.	1	1
Tissue Helix (THX-165-028) to bring tissue into the suturing window.	1	1
Suture-anchors (PLY-G02-020-APL or PLY-G02-020-A, depending on geography) to affect plications.	8	6
Cinch devices (CNH-G01-000) to lock the sutures in place.	8	6

The systems function by delivering the suture to the targeted area to create full thickness bites when approximating soft tissue. The representative final construct is shown in Figure 1, illustrating how the system approximates soft tissue.

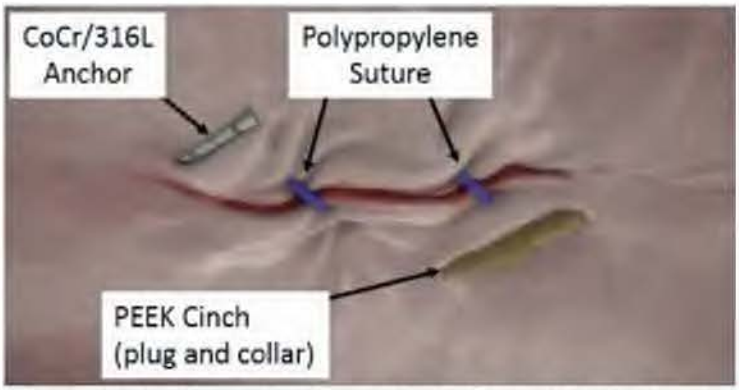

Figure 1: Representation of a final construct, including the polypropylene suture completing two stitches, and the anchor and cinch device components functioning as T-fasteners.

The device components are as follows:

- The OverStitch (SX) Handle is comprised of a needle driver assembly and anchor exchange (Figure 2). The end cap contains a needle body which exchanges an anchor with the anchor exchange to perform the stitching operations. The opening and closing of the suturing arm are controlled by the handle grip. The anchor exchange allows for the endoscopic loading and recapture of a suture-anchor assembly. Once the sutures are

placed, the anchor is released, allowing it to function as a tissue anchor, and the anchor exchange is removed.

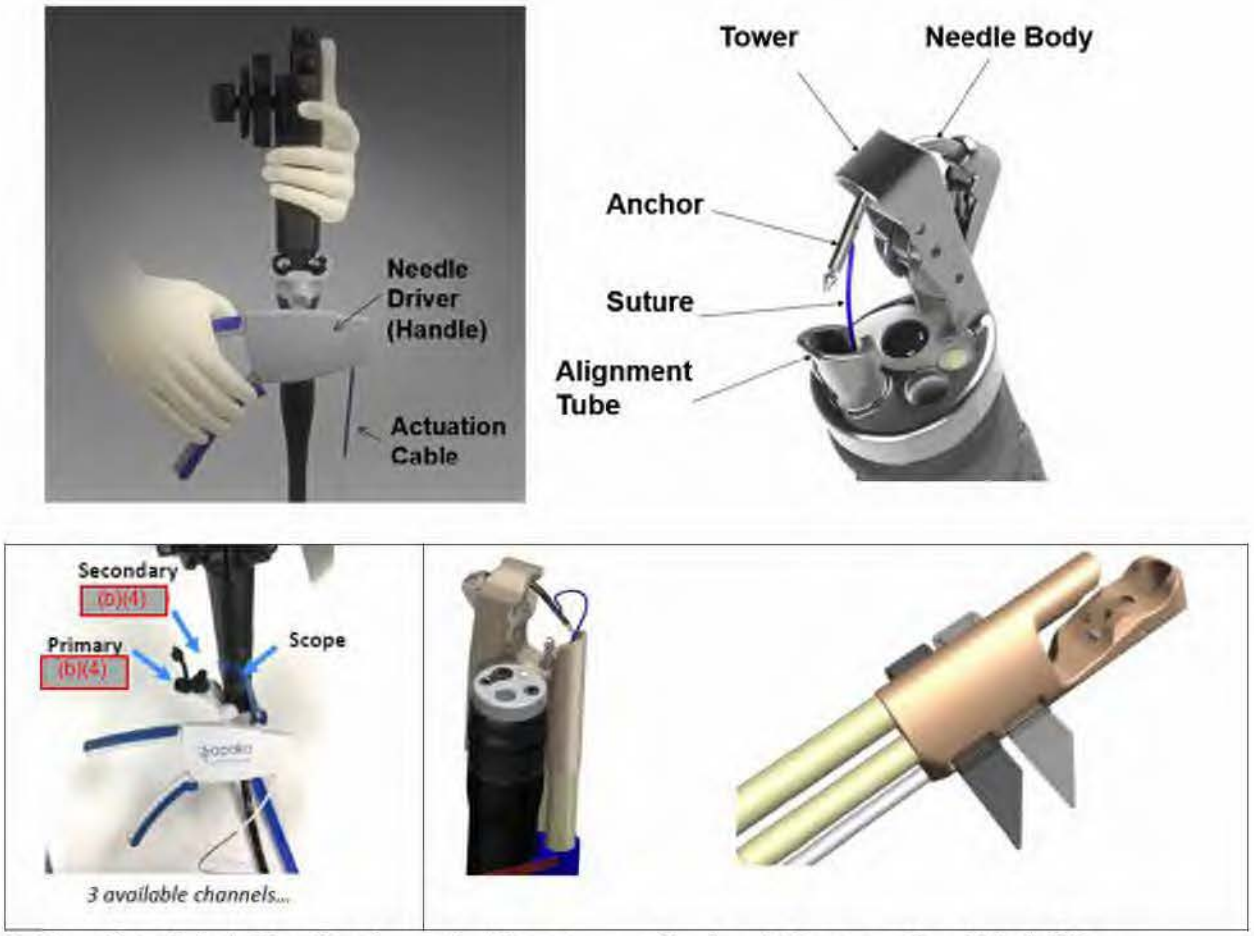

Figure 2: Top: OverStitch Handle pictured with suture at distal end. Bottom: OverStitch SX Handle pictured with suture and Tissue Helix at distal end.

- The Tissue Helix enables the user to manipulate and position tissue before and after suturing (Figure 3).

Figure 3: Top: general image of the Tissue Helix; bottom left: distal end of the Tissue Helix; bottom right: distal end of Tissue Helix shown in the endoscope channel with the OverStitch Handle.

- The Suture Anchor (Figure 4) consists of a polypropylene suture attached to a metal piece. The metal piece serves as the needle for piercing tissue and then as a pin (T-fastener) that holds tension on one end of the suture, in the final construct (see Figure 1).

Figure 4: Left: Suture Anchors as packaged; right: Suture-Anchor Assembly

- The Cinch device (Figure 5) is a plastic component that simultaneously cuts the suture and clamps onto the suture. It serves as a second T-fastener that holds tension on the other end of the suture, in the final construct (see Figure 1).

Figure 5: Cinch device

SUMMARY OF NONCLINICAL/BENCH STUDIES

The non-clinical/bench studies conducted on the APOLLO ESG, ESG SX, REVISE and REVISE SX Systems are summarized below. The APOLLO ESG, ESG SX, REVISE and REVISE SX Systems are identical in design to the OverStitch Systems previously cleared for marketing (K081853, K171886, K181141, K191439, and K210266) for a different intended use. Notations of non-clinical information that were relied upon and/or leveraged from prior marketing submissions to support the De Novo request are summarized in the information below.

STERILITY AND SHELF LIFE

The APOLLO ESG, ESG SX, REVISE and REVISE SX Systems are provided sterile and intended for single patient use. Documentation previously submitted to FDA in marketing submissions (K081853, K171886, K191439, and K210266) regarding ethylene oxide sterilization validation, bacterial endotoxin testing, and package integrity is applicable to the subject device systems and supports that the device systems have a sterility assurance level (SAL) of (b)(4) and can maintain sterility for the duration of the labeled shelf life.

Packaging integrity was evaluated in accordance with the following industry standards to confirm the packaging design provides an adequate protective barrier.

- ASTM D4169-16- Standard Practice for Performing Testing of Shipping Containers and Systems
- ASTM F2096-11- Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization
- ASTM F88/F88M-15- Standard Test Method for Seal Strength of Flexible Barrier Materials
- ASTM F1980-16) Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

Functional testing previously submitted to FDA in marketing submissions (K171886, K191439, K210266) supports that the device systems can function for duration of the labeled shelf life. Stability studies on aged devices included evaluations of device mechanical strength and comprehensive functional testing as outlined in Table 3.

BIOCOMPATIBILITY

APOLLO ESG, ESG SX, REVISE and REVISE SX System components: OverStitch (SX) Handle, Tissue Helix, and Cinch device are classified as mucosal membrane contacting for limited duration (≤ 24 hours).

APOLLO ESG, ESG SX, REVISE and REVISE SX System Suture Anchors are classified as breached or compromised surface contacting for permanent duration (> 30 days).

To support biocompatibility, appropriate biocompatibility assessments in accordance with ISO 10993-1, Biological evaluation of medical devices, and FDA Guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing

within a risk management process" were leveraged from prior marketing submissions (K081853, K171886, K181141, K191439, and K210266).

Biocompatibility endpoints for the OverStitch (SX) Handle, Tissue Helix, and Cinch device were:

(b)(4)

Biocompatibility endpoints for the Suture Anchors (shown in Figure 1) were:

(b)(4)

Results previously assessed by FDA support the biocompatibility of the APOLLO ESG, ESG SX, REVISE and REVISE SX Systems when used to place up to eight sutures and cinches.

PERFORMANCE TESTING - BENCH

The integrity and performance of the APOLLO ESG, ESG SX, REVISE and REVISE SX Systems were evaluated with the nonclinical bench testing summarized in Table 3.

Table 3: Summary of Performance Testing – Bench Studies

Test	Test Methods	Acceptance Criteria	Results
Durability of APOLLO Systems	(b)(4) suture passes were done during simulated use on synthetic tissue with a thickness of (b)(4)	APOLLO System can deliver 64 suture passes	Pass
Durability of Tissue Helix	(b)(4) iterations of grabbing and retracting synthetic tissue to demonstrate that the tip did not dull and the helix was not adversely affected such that it could not engage or release the tissue	Complete at least 64 tissue acquisitions	Pass
Magnetic Resonance Imaging (MRI) compatibility of implanted suture	Testing was conducted in accordance with ASTM F2052-02: Standard Test Method for Measurement of	MRI compatibility labeling must be supported by testing. To be considered MRI conditional, displacement forces should not have the potential to	Sutures are MRI conditional

Test	Test Methods	Acceptance Criteria	Results
• Displacement force	Magnetically Induced Displacement Force on Passive Implants in the Magnetic Resonance Environment,	damage the tissue where the device is placed	
Previous testing leveraged from prior marketing submissions K171886 and K191439			
APOLLO Systems Design verification	(b)(4)	• System can be passed through the working channel of an endoscope and can be manipulated within the endoscope • System allows for a 360 degree full range of motion on the endoscope • System can be passed through the working channel of an endoscope and can be visualized by the endoscope • System can be pre-loaded with an anchor-suture prior to passing the device endoscopically • System can be reloaded with a needle and suture endoscopically • System can obtain tissue to pass suture through tissue • Tissue Helix can be advanced up to collar and retracted into the endoscope without failure • System can deliver a suture through various tissue • Anchor-suture assembly placement can be visually confirmed endoscopically • System can secure a suture through the working channels of an endoscope • The Cinch attachment strength, for all suture types, shall maintain a minimum suture retention force of 2.4 lbf.	Pass
Polypropylene suture verification	• Suture-needle attachment (b)(4) • Tensile Strength (b)(4) (b)(4) • Suture diameter (b)(4) (b)(4)	• The tensile strength for the Anchor to the Suture in a T-tag configuration must be ≥ 1.10 kgf • The average knot-pull tensile strength of the Suture must be ≥ 1.44 kgf • The average Suture diameter must be between 0.300 mm and 0.339 mm. • The force required to pull 6 inches of suture through the endoscope (or Anchor Exchange Channel for SX designs) shall be less than 0.9 lbf.	Pass

Test	Test Methods	Acceptance Criteria	Results
MRI compatibility of implanted suture • Magnetically induced heating • Artifact assessment	ASTM F2182-02a: Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging, and ASTM F2119-01: Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants	MRI compatibility labeling must be supported by testing. To be considered MRI conditional, temperature increases should not damage tissues when patients are scanned as outlined in the labeling	Sutures are MRI conditional

SUMMARY OF CLINICAL INFORMATION

Clinical data from a pivotal study (MERIT Trial), real-world registry data, peer-reviewed literature, and post-market surveillance were leveraged to evaluate the safety and effectiveness of the APOLLO ESG, ESG SX, REVISE and REVISE SX Systems.

MERIT Trial

The Multi-center ESG Randomized Interventional (MERIT) Trial (ClinicalTrials.gov, NCT03406975) evaluated the effectiveness and safety of ESG as an adjunct to life-style intervention for weight loss compared to lifestyle intervention alone in participants 21-65 years of age with BMI ≥30 and ≤40 kg/m^2 who had failed to achieve and maintain weight loss with a non-surgical program. The study aimed to enroll at least 50 patients with hypertension, at least 50 with Type II diabetes mellitus (T2DM), and to enroll no more than 50 patients with no weight-related comorbidities.

This was a prospective, randomized, multicenter study and subjects were followed for two years. Patients were randomized in a 1:1.5 ratio of treatment (ESG + lifestyle modification) to control (lifestyle modification). At one year, patients in the Control group were allowed to cross-over to ESG if they had not responded to lifestyle modification (defined as not having achieved ≥25% Excess Weight Loss (EWL[1])) and had completed their follow-up visits.

The multicenter study (9 U.S. sites) was sponsored by the MAYO Clinic (Rochester, MN) and financial support was provided by Apollo Endosurgery, Inc. as part of a collaborative research agreement. The study data were compiled by the MAYO Clinic and provided to Apollo Endosurgery for independent analysis. Apollo's analysis of the MERIT Trial outcomes were used to support a reasonable assurance of safety and effectiveness.

[1] Excess Body Weight Loss (EWL), which assumes an ideal BMI of 25 kg/m^2 and uses height (h) measured in inches, was calculated as follows: ideal weight(lb.) = (25 x h^2)/703; excess weight (lb.) = initial weight (lb.) – ideal weight (lb.); %EWL = [TBWL (lb.)/(excess weight (lb.)] x 100%

Endpoints

The population for the effectiveness analysis was the modified intent-to-treat (mITT) population, which included all eligible subjects regardless of adherence to follow-up visits or the treatment program. The mITT population was defined as follows:

- Subjects in both groups that met the eligibility criteria for the study.
    - Treatment subjects that had an esophagogastroduodenoscopy (EGD) with confirmation of satisfying anatomical and medical criteria and completed the ESG.
    - Treatment and Control subjects that were confirmed ineligible based upon baseline visit information, were excluded from study analysis, even if the subject completed study visits prior to exclusion.
- Subjects in the Control group that completed at least one follow-up visit following randomization.

The population for the safety analysis included all patients that were assigned to have an ESG procedure, either as randomized or as a cross-over from lifestyle intervention alone to the ESG group.

The Completers population is defined as those mITT subjects that completed the 52-week visit.

Primary Effectiveness endpoint

The primary effectiveness endpoint of Apollo's analysis was the percentage of subjects who were responders to treatment at 52 weeks follow-up, where response was defined as achieving ≥10% Total Body Weight Loss (%TBWL[2]). The %TBWL was derived at each post-placement study visit for each subject where a weight measurement was collected.

Primary Safety endpoint

The primary safety endpoint was the percentage of subjects having device and procedure related adverse events with Clavien-Dindo[3] Grade III or higher at 52 weeks following ESG treatment. Grade III events require surgical, endoscopic, and/or radiological intervention; Grade IV events are life-threatening; and death is the Grade V event. All adverse events were recorded.

Secondary endpoints

Secondary endpoints collected as part of Apollo's analysis included %EWL and change in BMI from baseline. Along with %TBWL, these data were collected at each visit and used to evaluate the effectiveness of Treatment and Control, retightening of an ESG, and crossing over from lifestyle modification to ESG, over time.

Subject disposition

259 subjects provided informed consent and 209 subjects were randomized: 85 Treatment and 124 Control. Eight subjects in the Treatment group did not receive treatment, because they did not meet eligibility criteria; they were removed from the study. Twelve subjects in the Control

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[2] Percent Total Body Weight Loss (%TBWL), was calculated as follows: [(final weight (lb.) – initial weight (lb.)) / (initial weight (lb.))] X 100%

[3] Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery*, 240(2), 205.

group did not complete any study visits and were removed from the study. Two additional Control subjects were determined to be ineligible prior to starting the study. As a result, 77 Treatment and 110 Control subjects received the assigned treatment. Three Treatment subjects withdrew consent prior to the 52 week visit and six were lost to follow-up. In the Control group, 13 withdrew consent and eight were lost to follow-up prior to completing the 52 week visit. As a result, there were 68 Treatment and 89 Control subjects with effectiveness data at 52 weeks (Figure 6). Of the subjects with data at 52 weeks; 55 and 113 had baseline comorbidities of T2DM or hypertension, respectively, defined as a having a pre-existing diagnosis from their primary care physician and currently taking medications specifically for that comorbidity. Of those, 37 subjects had both baseline diagnosis of both diabetes and hypertension.

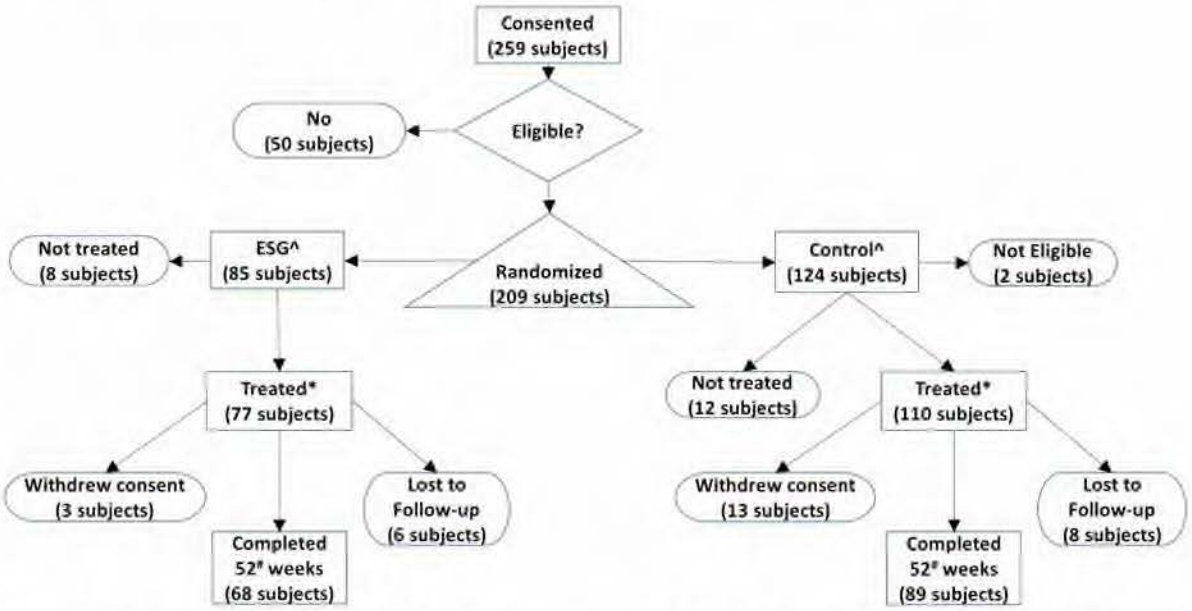

Figure 6: Schematic overview of subject accounting for each randomized group from consent through 52 weeks follow-up. The ITT population for each randomized group is identified by '^', the mITT population for each randomized group is identified by '*' and the completers population is identified by '#'.

At the conclusion of the first year of treatment, 89 Control subjects were evaluated for progression to the cross-over ESG procedure. A visual overview of the subject population for the cross-over subject follow-up is provided in Figure 7. Control subjects were ineligible for the cross-over ESG if they were found to be ineligible at the time of the EGD and the procedure was terminated before the device was introduced into the subject.

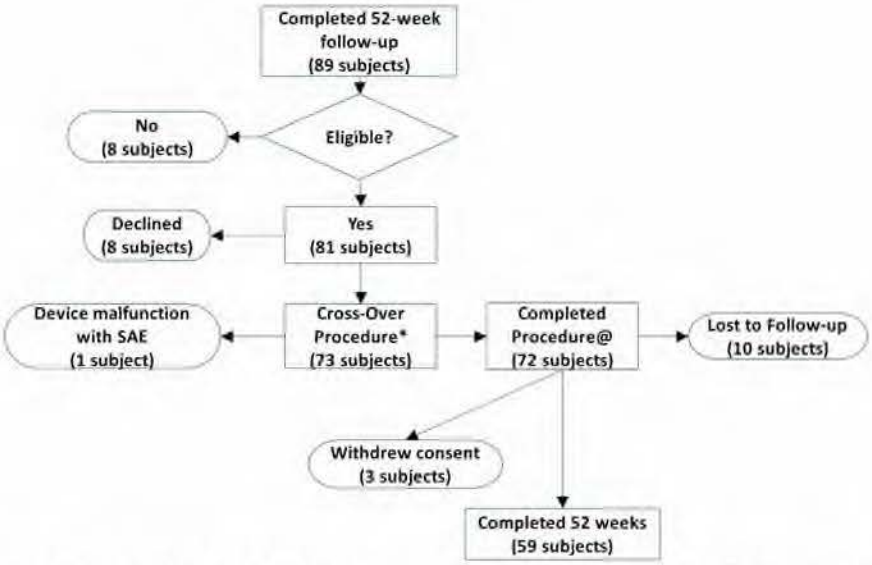

Figure 7: Schematic overview of subject accounting for follow-up for the cross-over ESG group through 52 weeks follow-up. The safety population is identified with a '*' as the device was used for all these subjects. Subjects that completed the procedure are considered the effectiveness population, as identified with a '@'.

Per Figures 6 and 7, 150 subjects had the ESG procedure (77 Treatment subjects and 73 Control subjects in the cross-over ESG group). These 150 subjects are the safety population of the MERIT Trial.

At the conclusion of the first year of treatment, 68 Treatment subjects were available to continue another year of follow-up. Of these subjects, 18 underwent an EGD for potential retightening. Fourteen subjects were retightened, 9 of these subjects were eligible per the protocol requirements and 5 subjects were not eligible per protocol (protocol deviations). Four were not retightened because they had intact plications. A visual overview of the subject population for the extended treatment follow-up, including subjects that underwent retightening procedures, is provided in Figure 8. The treatment group with extended follow-up had 59 subjects complete the additional 52-week visit (104 weeks total).

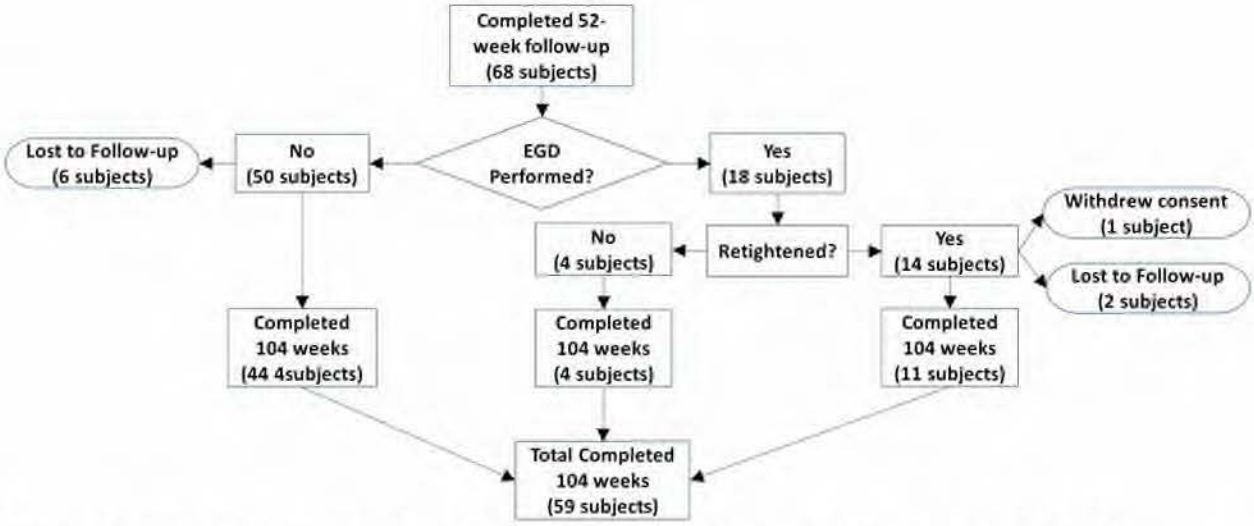

Figure 8: Schematic overview of subject accounting for follow-up beyond 52 weeks for Treatment group subjects. The diagram identifies the number of subjects that underwent an EGD following the 52-week visit and the retightening status of the subjects.

Study population demographics

Nine sites enrolled a total of 187 subjects that made up the modified Intent to Treat (mITT) population: 77 Treatment and 110 Control subjects. Table 4 provides demographic information.

Table 4: Demographics for mITT Population by Randomized Treatment Group

Description	Control (Lifestyle Modification)	Treatment (ESG + Lifestyle Modification)	p-value
N	110	77	
Weight (kg)			
Mean ± StdDev	99.2 ± 12.775	98.1 ± 12.346	0.641
Median	97.5	95.3	
Min, Max	73.8, 138.7	74.4, 130.0	
95% CI	96.7, 101.6	95.3, 100.9	
BMI (kg/m²)			
Mean ± StdDev	35.74 ± 2.6167	35.37 ± 2.5654	0.357
Median	35.78	35.52	
Min, Max	30.12, 39.88	31.01, 39.83	
95% CI	35.25, 36.24	34.79, 35.96	
Age (years)			
Mean ± StdDev	45.7 ± 10.072	47.3 ± 9.323	0.269
Median	45.5	49.0	
Min, Max	23, 65	22, 64	
95% CI	43.8, 47.6	45.22, 49.45	
Gender			
Male	17 (15.5%)	9 (11.7%)	0.525
Female	93 (84.5%)	68 (88.3%)	
Race			
White	62 (56.4%)	53 (68.8%)	0.136

African American	14 (12.7%)	11 (14.3%)	
Asian	3 (2.7%)	0 (0.0%)	
Hispanic / Latino	18 (16.4%)	11 (14.3%)	
Other	9 (8.2%)	1 (1.3%)	
Deferred	4 (3.6%)	1 (1.3%)	
Weight Related Comorbidities*			
T2DM	36 (32.7%)	19 (24.7%)	0.234
Hypertension	72 (65.5%)	41 (53.2%)	0.093

*For Apollo's analysis, the assignment to T2DM and/or hypertension was based on an existing diagnosis from the patient's primary healthcare provider combined with taking medication specifically for that diagnosis. Subjects could be identified as having both TY2DM and hypertension.

Effectiveness results

The primary effectiveness analysis is reported in Table 5. Responder rates at 52 weeks, as defined by achieving ≥10 %TBWL, in the completers population were 64.7% and 4.5% in Treatment and Control groups, respectively. Sensitivity analysis, including Last Observation Carried Forward, and Best and Worst Case Scenarios for missing data imputation, all showed a higher responder rate in the Treatment group compared to Control group. A tipping analysis was also performed to identify the number responders in each group that would no longer result in a significant difference between the two groups. The tipping analysis indicated that an additional 22 control subjects would need to be responders, or 17 fewer treatment subjects would need to be non-responders to tip the results of the analysis.

Table 5: Responder rates at 52 weeks, based on achievement of 10%TBWL in the mITT population.

Population	Control	Treatment	Difference	Standard Error of Difference	95% CI*	p-value
Completers						
Rate	4/89 (4.5%)	44/68 (64.7%)	-60.2%	6.2%	-71.0, -46.6	<0.001
CI (95%)	1.2, 11.1	52.2, 75.9				
LOCF						
Rate	5/110 (4.5%)	48/77 (62.3%)	-57.8%	5.9%	-68.2, -45.2	<0.001
CI (95%)	1.5, 10.3	50.6, 73.1				
Best Case Scenario						
Rate	25/110 (22.7%)	53/77 (68.8%)	-46.1%	6.6%	-58.0, -32.2	<0.001
CI (95%)	14.8, 32.5	57.3, 78.9				
Worst Case Scenario						
Rate	25/110 (22.7%)	44/77 (57.1%)	-34.4%	6.9%	-47.2, -20.3	<0.001
CI (95%)	15.3, 31.7	45.4, 68.4				

LOCF = last observation carried forward. Best case was calculated assuming that all Treatment and Control subjects lost to follow up were responders. Worst case scenario was that all Treatment subjects lost to follow-up were non-responders but all control subjects lost to follow-up were responders.

* Confidence interval was obtained based on the Agresti-Caffo confidence interval method, without multiplicity adjustment made.

Additional analyses were performed to report responder rates at 52 weeks (10% TBWL) by various subgroups. Table 6 below shows that responder rates across the subgroups defined by

age, gender, race, BMI, type II diabetes, and hypertension at baseline in the completers population were all higher in the Treatment group than in the Control group.

Table 6: Sub-group responder rates at 52 weeks based on achievement of at least 10% TBWL in the Completers population.

Comparison	Sub-Group	Control	Treatment	Difference	Standard Error of Difference	95% CI* (%)
Age	< 50 years	3/66 (4.5%)	22/37 (59.5%)	-54.9%	8.5%	-69.5, -36.7
	≥ 50 years	1/23 (4.3%)	22/31 (71.0%)	-66.6%	9.2%	-80.6, -42.8
Gender	Male	0/11 (0%)	6/9 (66.7%)	-66.7%	15.7%	-87.8, -24.0
	Female	4/78 (5.1%)	38/59 (64.4%)	-59.3%	6.7%	-70.9, -44.5
BMI	<35 kg/m^2	3/41 (7.3%)	24/31 (77.4%)	-70.1%	8.5%	-83.5, -49.5
	≥ 35 kg/m^2	1/48 (2.1%)	20/37 (54.1%)	-52.0%	8.4%	-66.4, -33.3
Race	Caucasian	3/51 (5.9%)	34/47 (72.3%)	-66.5%	7.3%	-78.4, -49.4
	Non-Caucasian	1/38 (2.6%)	10/21 (47.6%)	-45.0%	11.2%	-64.3, -21.3
Type II Diabetes	Yes	0/27 (0%)	11/18 (61.1%)	-61.1%	11.5%	-79.0, -34.1
	No	4/62 (6.5%)	33/50 (66.0%)	-59.5%	7.4%	-72.1, -43.1
Hypertension	Yes	1/55 (1.8%)	22/37 (59.5%)	-57.6%	8.3%	-71.6, -39.3
	No	3/34 (8.8%)	22/31 (71.0%)	-62.1%	9.5%	-77.3, -39.8

* Confidence interval was obtained based on the Agresti-Caffo confidence interval method, without multiplicity adjustment made.

The mean %TBWL is shown for each follow up visit in Table 7. Subjects in the Treatment group began to lose weight as early as the one week visit. Weight loss steadily progressed through 24 weeks (14.70 ± 5.62 %TBWL) then plateaued, with minimal weight regain at 52 weeks (13.86 ± 8.06 %TBWL). Comparatively, subjects in the Control group experienced very little weight loss through 52 weeks (0.76 ± 4.97 %TBWL).

Table 7: %TBWL by Randomized Group and Visit for the mITT Population

Weeks	Descriptive	Control	Treatment	Difference*
1	Mean ± StdDev	0.43 ± 1.7946	-5.08 ± 3.9745	5.51 ± 0.4890
	N	103	76	
	Median	0.11	-4.61	
	Min, Max	-4.94, 4.89	-29.00, 1.89	
	95% CI	0.08, 0.78	-5.99, -4.17	4.54, 6.48
4	Mean ± StdDev	-0.08 ± 2.2065	-8.47 ± 3.9968	8.39 ± 0.5242
	N	92	72	
	Median	0.00	-8.03	
	Min, Max	-7.79, 5.86	-33.36, -1.32	
	95% CI	-0.54, 0.37	-9.41, -7.53	7.35, 9.43
8	Mean ± StdDev	-0.42 ± 2.7118	-11.09 ± 4.4888	10.67 ± 0.6079
	N	90	70	
	Median	-0.17	-10.96	
	Min, Max	-7.32, 6.06	-35.36, -3.64	
	95% CI	-0.99, 0.15	-12.16, -10.02	9.47, 11.88
12	Mean ± StdDev	-0.94 ± 3.1050	-13.14 ± 4.9838	12.21 ± 0.6588

Weeks	Descriptive	Control	Treatment	Difference*
	N	89	62	
	Median	-0.55	-11.83	
	Min, Max	-8.81, 4.44	-37.18, -3.88	
	95% CI	-1.59, -0.28	-14.41, -11.88	10.79, 13.62
	Mean ± StdDev	-1.36 ± 4.5586	-14.70 ± 5.6167	13.34 ± 0.8172
	N	85	70	
24	Median	-0.80	-13.51	
	Min, Max	-14.31, 7.49	-29.03, 0.36	
	95% CI	-2.34, -0.38	-16.04, -13.36	11.73, 14.96
	Mean ± StdDev	-0.76 ± 4.9711	-13.86 ± 8.0585	13.10 ± 1.1102
	N	89	68	
52	Median	-0.39	-12.88	
	Min, Max	-17.62, 9.91	-40.91, 6.84	
	95% CI	-1.81, 0.29	-15.81, -11.91	10.89, 15.30
	Mean ± StdDev	NA	-14.72 ± 7.9433	NA
	N		57	
60	Median		-13.66	
	Min, Max		-34.09, 1.08	
	95% CI		-16.82, -12.61	
	Mean ± StdDev	NA	-13.93 ± 7.4285	NA
	N		61	
72-76	Median		-12.40	
	Min, Max		-37.00, 0.05	
	95% CI		-15.84, -12.03	
	Mean ± StdDev	NA	-12.20 ± 8.5461	NA
	N		59	
104	Median		-11.29	
	Min, Max		-34.91, 8.13	
	95% CI		-14.43, -9.97	

* Difference = Control – Treatment and 95% CIs are not adjusted for multiplicity

The mITT populations also observed the same type of changes in %EWL and changes in BMI. At the 52 week visit, Treatment and Control subjects reported a loss of 49.81 ± 31.40 and 2.98 ± 17.97 %EWL, respectively. Similarly, BMI in Treatment and Control subjects reduced by 4.76 ± 2.57 and 0.26 ± 1.77 kg/m^2, respectively, at 52 weeks.

Table 8 presents the %TBWL at each follow up visit in patients that were assigned to the Control group but crossed over to the Treatment group at 52 weeks. As early as the 1 week visit, subjects that crossed over to ESG lost more weight than they had with lifestyle modification. Weight loss steadily progressed through 24 weeks then plateaued, with minimal weight regain at 52 weeks. This was the same pattern demonstrated by subjects randomized to ESG. After 52 weeks of lifestyle modification alone, these cross-over subjects lost 0.18 ± 4.47 %TBWL. Then, 52 weeks after crossing over to ESG, these same subjects had lost 12.95 ± 8.64 %TBWL.

Table 8: %TBWL Control and Cross-Over

Weeks	Description	Control	Cross-Over	Difference*
1	Mean ± StdDev	0.38 ± 1.494	-4.38 ± 2.165	4.75 ± 0.315
	N	67	71	
	Median	0.24	-4.32	
	Min, Max	-3.89, 4.89	-10.27, 0.50	
	95% CI	0.01, 0.74	-4.89, -3.87	4.13, 5.38
4	Mean ± StdDev	0.12 ± 1.820	-7.70 ± 2.978	7.82 ± 0.423
	N	63	70	
	Median	0.00	-7.38	
	Min, Max	-4.37, 4.78	-16.05, 6.43	
	95% CI	-0.34, 0.57	-8.41, -6.99	6.98, 8.66
8	Mean ± StdDev	-0.34 ± 2.518	-10.35 ± 2.855	10.74 ± 0.610
	N	64	68	
	Median	-0.55	-10.45	
	Min, Max	-6.49, 5.09	-17.68, -4.05	
	95% CI	-0.97, 0.29	-11.04, -9.66	9.07, 10.93
12	Mean ± StdDev	-0.77 ± 2.936	-11.50 ± 4.097	10.91 ± 4.786
	N	67	69	
	Median	-0.55	-10.29	
	Min, Max	-8.58, 4.44	-28.77, -4.27	
	95% CI	-1.48, -0.05	-12.49, -10.52	9.53, 11.94
24	Mean ± StdDev	-0.69 ± 3.910	-13.35 ± 5.77	12.66 ± 0.849
	N	64	69	
	Median	-0.14	-12.28	
	Min, Max	-12.97, 7.49	-32.36, -3.83	
	95% CI	-1.67, 0.28	-14.74, -11.97	10.98, 14.34
52	Mean ± StdDev	-0.18 ± 4.473	-12.95 ± 8.636	12.77 ± 1.242
	N	72	59	
	Median	-0.02	-12.17	
	Min, Max	-17.62, 7.11	-36.64, 4.09	
	95% CI	-1.23, 0.87	-15.20, -10.70	10.30, 15.24

* Difference = Control – Treatment and 95% CIs are not adjusted for multiplicity

The cross-over population also demonstrated the same type of changes in %EWL and changes in BMI. At the 52 week visit after cross-over, subjects reported a loss of 46.85 ± 37.97% compared to 0.44 ± 15.34% EWL over the 52 weeks of lifestyle modification prior to crossing over. Similarly, BMI reduced by 4.59 ± 2.10 kg/m^2 52 weeks after crossing over, compared to a reduction of just 0.07 ± 1.61 kg/m^2, after the 52 weeks of lifestyle modification prior to crossing over. The weight loss from subjects following cross-over was consistent with the amount of weight loss in subjects randomized to the Treatment group.

Fourteen ESG patients had a secondary procedure to retighten the original ESG procedure. At 52 weeks prior to the retightening procedure, mean weight loss was 3.84 ± 4.31% TBWL in 9 subjects that had not experienced at least 25% EWL, and 10.94 ± 3.02% TBWL in 5 subjects that had lost more than 25% EWL. This is compared to 15.8 ± 7.5% TBWL in the 54 Treatment subjects still under study at 52 weeks that were not retightened. At 104 weeks, 52 weeks after retightening, the mean weight loss from baseline (index ESG procedure) was 7.10 ± 5.1% TBWL in the < 25% EWL group (9 subjects) and 11.6 ± 7.6% TBWL in the > 25% EWL group

(5 subjects). Similarly, %EWL and change in BMI were greater for the subjects with >25% EWL prior to the retightening procedure.

Safety results

The safety population includes subjects from both the initial ESG group (Figure 6, 77 subjects) and cross-over ESG group (Figure 7, 73 subjects) for a total of 150 subjects. Of these 150 subjects, 146 and 131 subjects had complete safety data through 24 and 52 weeks since the ESG, respectively.

The primary safety endpoint was the percentage of subjects having device and procedure related adverse events with Clavien-Dindo Grade III or higher at 52 weeks following ESG treatment. All adverse events were recorded.

There were 935 device or procedure related adverse events reported in the study. Of the 150 subjects that had an ESG (including primary and cross-over subjects), 138 (92%) experienced at least one device or procedure related adverse event and 132 (88%) experienced at least two adverse events. Some subjects reported multiple instances of a given type of adverse event.

The observed rate of device or procedure related, Clavien-Dindo[4] Grade III or higher, events was 2.3% (3/131) in the Completer population and the upper limit of the 1-sided 95% confidence interval was 6.5%. **Error! Reference source not found.** summarizes the primary safety endpoint analysis and provides imputations for the safety population, indicating a rate between 2.0% and 14.7% for a best case and worst case scenario..

Table 9: Primary Safety Endpoint: Incidence of Device and/or Procedure Related, Clavien-Dindo Grade III or higher, through 52 Weeks.

Analysis Population	Weeks	Incidence Rate	Upper Limit of 1-sided 95% CI*
Completers	52	3 / 131 (2.3%)	6.5%
Imputation (Best Case)	52	3 / 150 (2.0%)	5.7%
Imputation (Worst Case)^	52	22 / 150 (14.7%)	21.4%

^ Worst case scenario assumed that subjects with missing data had a safety endpoint event. Subjects that continue in active follow-up and have completed their 24-week visit were not reported as an SAE in Worst Case as all reported SAEs occurred prior to the 12 week visit. This ensures that subjects that continue to be followed but are not yet due for their expected visits do not negatively impact the imputation.

* Confidence interval was obtained based on the Agresti-Caffo confidence interval method, without multiplicity adjustment made.

The three adverse events rated Clavien-Dindo Grade III or higher were as follows:

- One patient presented with an abdominal abscess and plural effusion two weeks after ESG.
- One patient was admitted at 11 weeks following ESG with weakness, dehydration, altered mental status and was suspected of malnutrition.
- One patient was kept in the hospital after the ESG due to abdominal pain, nausea and vomiting. It was determined that this patient had bleeding associated with the use of

[4] Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery*, 240(2), 205.

argon plasma coagulation to mark the intended suture locations. This patient was found to have clotted blood, which was located in the cardia (between the stomach and esophagus).

All three cases resolved with medical intervention.

An additional safety analysis was performed for the rate of serious adverse events (SAEs; Table 10). There were 21 device or procedure related SAEs reported from 11 of the 150 subjects receiving ESG (including primary and cross-over subjects). This an SAE rate of 7.3% (11/150; 95% CI: 3.7-12.7%). See **Error! Reference source not found.**. The most frequently reported SAEs were nausea, abdominal pain and vomiting. Seven patients were hospitalized after the ESG procedure to address early post-operative symptoms associated with accommodation to the sleeve, primarily nausea and vomiting. Treatments consisted of intravenous fluids, pain medications and anti-emetics and all adverse events resolved prior to discharge. There was also a device-related SAE during a cross-over ESG procedure that resulted in a mucosal tear in the esophagus and the decision was made to not complete the procedure. The patient was kept in the hospital for three days and then discharged.

Table 10:Device and/or Procedure Related Serious Adverse Events

Serious Adverse Event[1]	**# Subjects (%)**	**# Events**	**Onset (days to event)**
Abdominal Abscess	1/150 (0.7%)	1	15
Abdominal Pain	3/150 (2.0%)	3	Mean = 1.7 Median = 2 Range = 0-3
Bloody Stools	1/150 (0.7%)	1	0
Bowel Impaction	1/150 (0.7%)	1	81
Dehydration	1/150 (0.7%)	1	5
Esophageal Mucosal Tear	1/150 (0.7%)	1	0
GI bleeding at argon plasma coagulation site	1/150 (0.7%)	1	0
Malnutrition[2]	1/150 (0.7%)	1	77
Nausea	5/150 (3.3%)	5	Mean = 0.8 Median = 1 Range = 0-2
Pleural Effusion	1/150 (0.7%)	1	20
Pneumonitis	1/150 (0.7%)	1	4
Sore Throat	1/150 (0.7%)	1	8
Vomiting	3/150 (2.0%)	3	Mean = 0.3 Median = 0 Range = 0-1
Total	11/150 (7.3%)	21	Mean = 11 Median = 2 Range = 0-81

[1] A serious adverse event is one that:

- Led to death
- Resulted in serious deterioration in the health of the subjects that results in:
  - Life-threatening illness or injury
  - Permanent impairment of a body structure or a body function
  - The need for in-patient care or prolongation of hospitalization (this does not include the optional 23 hours observation admission after ESG or re-tightening procedure)

- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Planned hospitalization for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event

[2] This patient that had their ESG reversed during the study.

Considering gastrointestinal adverse events that could be attributed to the device or procedure, the most common events were nausea, abdominal pain, constipation, eructation, heartburn and diarrhea (Table 11). These types of events tended to initiate within the first week of the procedure and to resolve within 30-60 days.

Table 11: Gastrointestinal Device and/or Procedure Related Adverse Events Occurring in > 10% of Subjects

Adverse Event	**# Subjects (%) N=150**	**Date of Onset: Median (Mean) Range**	**Duration in Days[1]: Median (Mean) Range**	**Severity[2] n/N (%): Mild[3] Moderate[4] Severe[5] Unknown[6]**	**# Subjects with onset <= 3 days post-procedure (%)**	**# Subjects with onset <= 3 post-procedure with duration > 14 days and <= 30 days (%)**	**# Subjects with onset <= day 3 post-procedure with duration > 30 days (%)**
Nausea	105 (70.0%)	0 9.5 0-365	3 7.7 1-89	76/105 (72.4%) 24/105 (22.8%) 5/105 (4.8%)	92/105 (87.6%)	3/92 (3.3%)	3/93 (3.3%)
Abdominal Pain[7]	102 (68.0%)	0 (37.5) 0-704	4 (16.1) 1-162	77/102 (75.5%) 22/102 (21.6%) 3/102 (2.9%) 0/102 (0%)	82/102 (80.4%)	8/82 (9.8%)	6/82 (7.3%)
Eructation[7]	77 (51.3%)	1 19.1 0-366	27 45.8 1-403	67/77 (87.0%) 10/77 (13.0%) 0/77 (0%) 0/77 (0%)	55/77 (71.4%)	5/55 (9.1%)	24/55 (43.6%)
Vomiting	74 (49.3%)	0 23.5 0-541	2 8.1 1-368	54/74 (73.0%) 16/74 (21.6%) 3/74 (4.1%) 1/74 (1.3%)	60/74 (81.1%)	0/60 (0%)	1/60 (1.7%)
Constipation[7]	68 (45.3%)	7 39.5 0-567	26 51.5 1-368	51/68 (75.0%) 17/68 (25.0%) 0/68 (0%) 0/68 (0%)	30/68 (44.1%)	3/30 (10.0%)	12/30 (40.0%)

Heartburn / Reflux	55 (36.7%)	2 40.1 0-550	10 44.5 1-253	40/55 (72.7%) 14/55 (25.5%) 0/55 (0%) 1/55 (1.8%)	34/55 (61.8%)	4/34 (11.8%)	9/34 (26.5%)
Diarrhea[7]	23 (15.3%)	8 65.3 0-427	8 25.7 1-296	20/23 (87.0%) 2/23 (8.7%) 0/23 (0%) 1/23 (4.3%)	9/23 (39.1%)	1/9 (11.1%)	1/9 (11.1%)

[1] Duration in Days = Date of Resolution – Date of Onset +1. Thus, an event that resolved the same day as onset will have a day of resolution = 1.
[2] Subjects with multiple events of the same type are reported by first occurrence with the highest severity
[3] Mild = awareness of sign or symptom, but easily tolerated, although not specifically defined in the study protocol
[4] Moderate = discomfort enough to cause interference with usual activity, although not specifically defined in the study protocol
[5] Severe = incapacitating with inability to work or do usual activity, although not specifically defined in the study protocol
[6] Unknown = no response was recorded in the electronic database.
[7] The following events did not have a resolution date recorded and were excluded from the duration calculations (1 report of Abdominal pain, 3 reports of constipation, 1 report of diarrhea, and 1 report of eructation).

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

Real-World Evidence

Real-world evidence used to support a reasonable assurance of safety and effectiveness included real-world registry data and published clinical literature.

Endoscopic sleeve gastroplasty (ESG)

A structured literature review was conducted to specifically identify all reported complications and adverse events that have been associated with ESG. Additionally, the literature review focused on the ability to perform revisions after ESG.

For the literature review, articles were retrieved from the PubMed database using the following search terms:

"endoscopic sleeve gastroplasty"[All Fields] OR "transoral outlet reduction"[All Fields] AND (("2017/01/01"[PDAT]: "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])

Duplicate articles were removed. A total of 51 articles were retrieved. Any publications that did not have sufficient information to be able to undertake a rational and objective assessment based on the appraisal of the full text article was not included in the clinical data analysis review; however, a review of the articles for safety data/incidents was performed. Inclusion/exclusion criteria for article screening are outlined below:

Inclusion

- Describes endoscopic sleeve gastroplasty or transoral outlet reduction

- OverStitch device

Exclusion

- Review articles that do not include clinical data
- Editorial articles

Nine additional articles were considered due to their relevance though they were not recovered via the PubMed search.[5,6,7,8,9,10,11,12,13]

The literature review supplements data from the MERIT Trial and supports the following statements.

- Common adverse events tend to happen early after the procedure, and tend to resolve.
- Clinically meaningful weight loss can be achieved via the ESG procedure.
- An ESG procedure can be reversed in cases where the patient cannot tolerate the sleeve.
- An ESG can be re-tightened in cases where the patient starts to regain weight after an initially successful result.
- An ESG can be revised to a laparoscopic sleeve gastrectomy (LSG) when needed.
- ESG can be performed to tighten a sleeve from (LSG).
- ESG may be performed in patients with BMI up to 50 kg/m^2.
- There is durability to the weight loss achieved following the ESG procedure.

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[5] Alhayo S & Devadas M. Case Report: Laparoscopic sleeve gastrectomy following multiple failed endoscopic sleeve gastroplasties. J Surgical Case Reports 2019;12, 1-3.

[6] Alqahtani A & Aljohani E. Case Report: Unusual presentation of rare complication following endoscopic gastroplasty case report. J Surgical Case Reports 2020;7, 1-3.

[7] Boskoski I, Pontecorvi V, Gallo C, Bove V, Laterza L, Costamagna G, Redo endoscopic sleeve gastroplasty: technical aspects and short-term outcomes. Therap Adv Gastroenterol. 2020 Jan 20;13:17562819896179. Doi: 10.1177/1756284819896179. eCollection 2020.

[8] Cheng Q, Tree K, Edye M, Devadas M, Reversal of endoscopic sleeve gastroplasty and conversion to sleeve gastrectomy – Two case reports. Int J Surg Case Rep. 2020;68:180-184. Doi: 10.1016/j.ijscr.2020.02/060. Epub 2020 Feb 29.

[9] Eid G. Sleeve gastrectomy revision by endoluminal sleeve plication gastroplasty: a small pilot case series. Surg Endosc. 2017 Oct;31(10):4252-4255. doi: 10.1007/s00464-017-5469-1. Epub 2017 Mar 31.

[10] Espinet-Coll E, Nebreda-Durán J, Galvao-Neto M, Bautista-Altamirano C, Diaz-Galán P, Gómez-Valero JA, Vila-Lolo C, Guirola-Puche MA, Fernández- Huélamo A, Bargalló-Carulla D, Comamala AJ-C, Suture pattern does not influence outcomes of endoscopic sleeve gastroplasty in obese patients. Endosc Int Open. 2020 Oct;8(10):E1349-E1358. Doi: 10.1055/a-1221-9835. Epub 2020 Sep 22.

[11] Lopez-Nava G, et al., Biliary peritonitis after endoscopic sutured gastroplasty for morbid obesity (with video), Gastrointest Endoscopy 90:4 (2019), p686-688.

[12] Mohan BP, Asokkumar R, Khan SR, Kotagiri R, Sridharan GK, Chandan S, Ravikumar NP, Ponnada S, Jayaraj M, Adler DG, Outcomes of endoscopic sleeve gastroplasty; how does it compare to laparoscopic sleeve gastrectomy? A systematic review and meta-analysis. Endosc Int Open. 2020 Apr;8(4): E558-E565. Doi: 10.1055/a-1120-8350. Epub 2020 Mar 23.

[13] Sharaiha RZ, Hajifathalian K, Kumar R, Saunders K, Mehta A, Ang B, Skaf D, Shah S, Herr A, Igel L, Dawod Q, Dawod E, Sampath K, Carr-Locke D, Brown R, Cohen D, Dannenberg A, Mahadev S, Shukla A, Aronne LF, Five-Year Outcomes of Endoscopic Sleeve Gastroplasty for the Treatment of Obesity, Clin Gastroenterol Hepatol. 2021 May;19(5):1051-1057.e2. doi: 10.1016/.cgh.2020.09.055. Epub 2020. Oct 1.

The meta-analysis data are consistent with the experience in a registry conducted by the American Gastroenterological Society and other registry data.[14,15]

Transoral outlet reduction (TORe)

Patients having previous Roux-en-Y gastric bypass bariatric surgery may experience dilation of the gastrojejunostomy outlet and the gastric pouch, followed by weight gain. This can be addressed by reducing the diameter of the gastric outlet by suturing. Often, the physician may elect to use additional suturing to reduce the dilated areas of the pouch. This procedure is often referred to as Transoral Outlet Reduction (TORe). These sutures can be applied using the APOLLO REVISE or APOLLO REVISE SX Systems.

The TORe procedure is appropriate when a previous bypass patient demonstrates a stoma diameter greater than 20 mm and the patient is regaining weight.[16] Meta-analysis of published data for 737 patients supports that the TORe procedure with full thickness suturing can reduce the stoma diameter to 8-10 mm and result in an average of 8.1-11.0% TBWL through 6 months and 4.3-7.1 %TBWL at 12 months.[17] A retrospective review of prospectively collected data on 331 Roux-en-Y gastric bypass patients who underwent TORe for weight regain or inadequate weight loss supports durability of the TORe procedure.[18]

The meta-analysis data are consistent with the experience in a registry conducted by the American Gastroenterological Society and other registry data.[19,20]

The most common risks reported as being associated with the TORe procedure are bleeding (associated with the use of plasma coagulation) and stricture of the outlet.

Post-market surveillance

The APOLLO ESG, ESG SX, REVISE and REVISE SX Systems are identical in design to the OverStitch Systems previously cleared for marketing for a different intended use (K081853, K171886, K181141 K191439, and K210266). FDA conducted a medical device report (MDR) analysis using the System for Uniform Surveillance (SUS). The focus was on endoscopic sleeve gastroplasty (ESG) and/or transoral outlet reduction (TORe). The results included 75 MDRs for the Apollo Overstitch by Apollo Endosurgery, Inc., procodes OCW and HCF. The reports were

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[14] A multicenter (15 sites) registry on endoscopic suturing conducted as a partnership between Apollo Endosurgery and the American Gastroenterological Association. The study included 80 subjects having the primary ESG procedure.

[15] An ongoing registry made available to Apollo Endosurgery, including 295 subjects enrolled at a private bariatric practice in the US and in Brazil. There is 6-month data for 169 patients and 12-month data for 116 patients at the time of FDA's review

[16] Abu Dayyeh BK, Lautz DB, Thompson CC. Gastrojejunal stoma diameter predicts weight regain after Roux-en-Y gastric bypass. Clinical Gastroenterology and Hepatology 2011; 9: 228-233.

[17] Jaruvongvanich V, Vantanasiri K, Laoveeravat P et al. Endoscopic full thickness suturing plus argon plasma coagulation versus argon plasma mucosal coagulation alone for weight regain after gastric bypass: a systematic review and meta-analysis. Gastro Endo 2020; 92(6): 1164-1175.

[18] Jirapinyo P, Kumar N, AlSamman MA et al. Five-year outcomes of transoral outlet reduction for the treatment of weight regain after Roux-en-Y gastric bypass. Gastrointest Endosc 2020; May;91(5):1067-1073.

[19] A multicenter (15 sites) registry on endoscopic suturing conducted as a partnership between Apollo Endosurgery and the American Gastroenterological Association. The study included 39 subjects having the TORe procedure.

[20] An ongoing single site registry made available to Apollo Endosurgery, including 201 subjects enrolled at a private bariatric practice. There is 6-month data for 89 patients and 12-month data for 30 patients at the time of FDA's review.

individually reviewed. Of the 75 relevant MDRs, the most frequent patient problem was internal organ perforation (5 MDRs) followed by abdominal pain (2 MDRs) and hemorrhage/intestinal hemorrhage (2 MDRs). The rest of the problems were only reported in one MDR each including death, sepsis, lacerations of the esophagus, pneumothorax, peritonitis, nausea, respiratory tract infection, pulmonary embolism, liver abscess, fever, and indeterminate tissue damage.

LABELING

Physician labeling includes the device indications for use, a description of the device, warnings and precautions, clinical data on the device, and instructions for the safe and effective use of the device. The labeling satisfies the requirements of 21 CFR 801.109 Prescription devices.

Per the Special Controls for this generic type of device, labeling includes a summary of device effectiveness and device related adverse events.

RISKS TO HEALTH

The table below (Table 12) identifies the risks to health that may be associated with use of an endoscopic suturing device for altering gastric anatomy for weight loss, and the measures necessary to mitigate these risks.

Table 12: Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Device- and/or procedure-related adverse events, including: • Death • Gastrointestinal bleeding • Obstruction • Perforation • Injury to organs adjacent to the stomach • Perigastric leak • Nausea • Infection • Pain • Pneumoperitoneum • Pneumothorax • Pulmonary embolism	Clinical performance testing Non-clinical performance testing Labeling Training Sterilization validation Shelf life testing
Weight gain	Clinical performance testing Labeling
Adverse tissue reaction	Biocompatibility evaluation

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the endoscopic suturing device for altering gastric anatomy for weight loss is subject to the following special controls:

(1) Clinical performance testing must demonstrate the device performs as intended under anticipated conditions of use and evaluate the following:
   (i) Weight change; and
   (ii) All adverse events.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   (i) Performance bench testing in a simulated use model must verify functional aspects of the device design and support device durability during clinical use;.
   (ii) Dimensional specifications must be verified; and
   (iii)Tensile strength testing must be performed for all articulating components.

(3) Performance data must support the shelf life of the device by demonstrating continued package integrity and device functionality over the labeled shelf life.

(4) Performance data must demonstrate the sterility of the patient-contacting components of the device.

(5) The patient-contacting components of the device must be demonstrated to be biocompatible.

(6) Training must be provided so that, upon completion of the training program, the user can use the device correctly to approximate tissue to alter the gastric anatomy for the purpose of weight loss with minimal impact to the safety of the patient.

(7) Labeling must include:
   (i) A summary of clinical performance testing with the device, including a discussion of adverse events and clinical benefit reported as percent total body weight loss; and
   (ii) A shelf life.

BENEFIT-RISK DETERMINATION

Nonclinical laboratory studies as well as clinical data from a pivotal study (MERIT Trial), real-world registry data, peer-reviewed literature, and post-market surveillance were leveraged to evaluate the safety and effectiveness of the APOLLO ESG, APOLLO ESG SX, APOLLO REVISE and APOLLO REVISE SX Systems.

Summary of Benefits

Clinical data support that the device can be used to facilitate the endoscopic sleeve gastroplasty (ESG) procedure. Through this procedure, the data supports that weight loss can be achieved. Thus, the device facilitates weight loss by reducing stomach volume through ESG. Data on the

durability of the ESG procedure for long-term outcomes beyond one year were not provided. Additional data support that the device can be used to facilitate transoral outlet reduction (TORe) for revision to Roux-en-Y gastric bypass. Following the TORe revision, patients are able to lose weight.

The company provided a pre-specified, post-hoc analysis of the MERIT trial. The primary effectiveness endpoint was based on the responder rate, defined as the proportion of patients having at least 10% total body weight loss (%TBWL) at 52 weeks after the ESG procedure. The difference of responder rates between the two study groups ranged from 60.2% (Completers population) to 35.1% (worst case scenario). The worst case scenario was that all Treatment subjects lost to follow-up were non-responders but all Control subjects lost to follow-up were responders. A tipping analysis was also performed to identify the number responders in each group that would no longer result in a significant difference between the two groups. The tipping analysis indicated that an additional 22 control subjects would need to be responders, or 17 fewer treatment subjects would need to be non-responders to tip the results of the analysis.

The mean %TBWL at 52 weeks was 13.86 ± 8.06% for Treatment subjects and 0.76 ± 4.97% for Control subjects. Thus, the difference was 13.10 ± 1.11% (95% CI: 10.89%, 15.30%) TWBL. This difference is believed to be clinically significant.

At the 52 week visit, Treatment and Control subjects reported a loss of 49.81 ± 31.40% and 2.98 ± 17.97% EWL, respectively. BMI in Treatment and Control subjects reduced by 4.76 ± 2.57 kg/m^2 and 0.26 ± 1.77 kg/m^2.

At one year, patients in the control lifestyle modification group were allowed to cross-over to ESG if they had not responded to lifestyle modification (defined as not having achieved ≥25% EWL) and had completed their follow-up visits. After 52 weeks of lifestyle modification alone, these crossover subjects lost 0.18 ± 4.47% TBWL. Fifty-two weeks after cross-over to ESG, these same subjects had lost 12.95 ± 8.64% TBWL.

Meta-analysis of published data supports that the TORe procedure using the APOLLO REVISE Systems can result in additional weight loss in patients who have regained weight after Roux-en-Y gastric bypass bariatric surgery due to dilation of the gastrojejunostomy outlet and the gastric pouch.

Factors that increase uncertainty in determining probable benefits for the APOLLO ESG, APOLLO ESG SX, APOLLO REVISE, APOLLO REVISE SX Systems include:

- The MERIT Trial analysis was done on a modified intent-to-treat (mITT) subset of enrolled subjects. Under ITT, study participants are analyzed as members of the treatment group to which they were randomized regardless of their adherence to, or whether they received, the intended treatment. Reported outcomes from the MERIT Trial are potentially biased at the level of adherence in the study.

- The withdrawal rate was 20% (17/85) for the Treatment group and 28% (35/124) for the Control group of randomized patients in the MERIT Trial. The large amount of missing data made the effectiveness analyses more dependent on the statistical models used.

- Primary outcome measurement of weight was done remotely for some patients during the MERIT Trial. SARS-CoV-2 and the associated lock-down of communities and elective medical care had an impact on this study. One of the biggest impacts is missing data from completed remote or telemedicine visits. Missing data included, but was not limited to: vital signs, blood chemistries, waist measurements, and consistent weight measurements from the same clinic scale. Cross-over ESG procedures were sometimes delayed 1 to 6 months. Approximately 10% of the visits in each study group are probable telemedicine. The cross-over group had approximately 30% or more probable telemedicine visits.

- The lifestyle modification program provided to Treatment and Control subjects was a low intensity program. A low-intensity lifestyle modification program is not anticipated to result in significant weight loss.[21] Considering that this patient population is refractory to weight loss via diet and exercise, there is limited value to the control arm intervention. The treatment effect of the APOLLO ESG and APOLLO ESG SX Systems in unknown relative to a robust lifestyle modification program.

- The baseline parameters were appropriately balanced between the Treatment group and the Control group in the MERIT Trial with the exception of baseline comorbidity status. However, there was a bias toward Caucasian female subjects with rates: 86.1% female, 61.5% white, 13.4% African-American, 1.6% Asian, and 15.5% Hispanic. The study population may not represent the patient population who are obese or overweight in the US.[22]

- Reports from the published literature are considered valid scientific evidence and provided evidence to support device benefit. However, there are certain limitations presented in the published reports from the literature, such as not containing complete clinical study plans, details about the conduct, accountability, and outcomes. Given such limitations, it may be difficult to determine the impact of bias on study findings. Aside from potential biases that arise in the study design, study conduct, or subject selection in clinical studies, there are additional sources of bias associated with published reports in the literature that need to be considered. For example, publication bias, which may occur when publication of study results depend on the significance of study findings, rather than the rigor of the clinical study. Literature reports are also often susceptible to post hoc analysis issues. That is, analyses are performed after the data have been looked at for any hypotheses that were not pre-specified. The impact of missing data is not often examined in literature reports. Even though missing data are unavoidable in any clinical study, it is important to note that missing data can potentially reduce the interpretability of study results and introduce potential substantial bias.

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[21] Jensen MD, *et al.* 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014;63:2985–3023.

[22] https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity

- Registry data from one clinical practice may not be wholly representative of the entire US population. Additionally, registry data from OUS locations (i.e., Brazil) may not be representative of outcomes in the US patient population.[23]

Summary of Risks

There were 935 device or procedure related adverse events reported in the Merit Trial. Of the 150 subjects that had an ESG (including primary and cross-over subjects), 138/150 (92%) experienced at least one device- and/or procedure-related adverse event and 132/150 (88%) experienced at least two. Considering gastrointestinal adverse events that could be attributed to the device or procedure, the most common events were nausea, abdominal pain, constipation, eructation, heartburn and diarrhea. All of these types of events tended to initiate within the first week of the procedure and resolved within 30-60 days.

There were 21 device or procedure related SAEs reported from 11 of the 150 subjects receiving ESG in the Merit Trial. This is an SAE rate of 7.3% (11/150; 95% CI: 3.7-12.7%). The most frequently reported SAEs were nausea, abdominal pain and vomiting. The observed rate of device- and/or procedure-related, Clavien-Dindo Grade III or higher, events was 2.3% (3/131) and the upper limit of the 1-sided 5% confidence interval was 6.5%. In a worst case scenario that all Treatment subjects lost to follow-up experienced a SAE: 20.0% (30/150; 95% CI upper bound of 28.0%) experienced a SAE; and 14.7% (11/150; 95% CI upper bound of 22.0%) experienced a Clavien-Dindo grade III or higher adverse event within 52 weeks of the ESG procedure.

Factors that increase uncertainty in determining probable risks for the APOLLO ESG, APOLLO ESG SX, APOLLO REVISE, APOLLO REVISE SX Systems include:

- The number of subjects treated with the APOLLO ESG and APOLLO ESG SX Systems in the Merit Trial was relatively small considering the potential use of these devices in clinical practice. Additionally, there were patients that were lost to follow up or withdrew from the study where the withdrawal rate was 11.6% (9/77 patients treated) for the initial Treatment group and 17.8% (13/73 patients treated) in the cross-over ESG group. The small sample size makes detection or more rare, but severe and/or serious adverse events difficult to detect and the anticipated rates are unknown.

- Published literature on the ESG and TORe procedures were used to understand risks to patients. Though helpful, reports from the literature can be subject to bias as discussed above regarding uncertainty associated with clinical benefit. Complete safety reporting is not always a primary aim of the published literature.

- Some of the registry data provided are from a single-surgeon practice. The use of registry data from a single-surgeon practice to support the use of APOLLO ESG and APOLLO

[23] An ongoing registry made available to Apollo Endosurgery, including 295 subjects enrolled at a private bariatric practice in the US and in Brazil. There is 6-month data for 169 patients and 12-month data for 116 patients at the time of FDA's review.

REVISE systems may not be representative of the normal skill and device familiarity of the greater population of practicing gastroenterologists.

- Post-market surveillance information from MDRs helped support a reasonable assurance of safety as it served as an additional foundation for identification of probable risks. Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use.

Patient Perspectives

The data provided did not include specific information on patient perspectives; however adverse events reported by patients in the MERIT Trial (as reported above) were considered in FDA's benefit/risk assessment.

Benefit/Risk Conclusion

In the MERIT Trial, the primary endpoint demonstrates a clinical benefit in weight loss. There is moderate uncertainty in the benefit. Subjects undergoing ESG with the APOLLO ESG System in tandem with a low intensity lifestyle modification program lost on average ~14% of their baseline weight compared to ~1% weight loss in subjects provided a low-intensity lifestyle modification program alone at 52 weeks post-ESG procedure. About 62% of subjects who had an ESG using the APOLLO ESG and APOLLO ESG SX Systems lost at least 10% of their baseline weight. Worst case scenario assessment of MERIT Trial data also support weight-loss benefit.

Information provided support that use of the APOLLO REVISE Systems for TORe to revise a previous Roux-en-Y gastric bypass bariatric surgery can reduce the stoma diameter to 8-10 mm and result in an average of 8.1-11.0% TBWL through 6 months and 4.3-7.1 %TBWL at 12 months.

The safety profile for the APOLLO ESG, APOLLO ESG SX, APOLLO REVISE, APOLLO REVISE SX Systems is acceptable, with 11 subjects experiencing 21 device- or procedure-related SAEs among 150 subjects in whom the ESG procedure was attempted in the MERIT Trial.

Patients with obesity need treatment options and are willing to accept risk or varied amounts of weight loss.[24] Options for patients with obesity other than diet and exercise include pharmacotherapy, weight-loss devices, and bariatric surgery (stomach restricting and/or malabsorptive procedures). The device is intended to perform ESG, which is a different approach to the laparoscopic sleeve gastrectomy (LSG) or traditional gastric bypass. Additionally, the device fills a treatment niche for lower BMI individuals (under BMI 40 kg/m^2) who would otherwise not be a candidate for a surgical weight loss procedure.

[24] Ho, M. et al (2015). Incorporating patient-preference evidence into regulatory decision making. Surgical endoscopy, 29(10), 2984-2993

In conclusion, the probable benefits outweigh the probable risks for the APOLLO ESG, APOLLO ESG SX, APOLLO REVISE, APOLLO REVISE SX Systems when used as part of ESG and/or TORe procedures in patients with BMI between 30.0 and 50.0 kg/m^2 when users are properly trained on device use for these procedures. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the APOLLO ESG, APOLLO ESG SX, APOLLO REVISE, APOLLO REVISE SX Systems is granted and the device is classified as follows:

Product Code: QTD
Device Type: Endoscopic suturing device for altering gastric anatomy for weight loss
Regulation Number: 21 CFR 876.5983
Class: II