**Swallowable Gas-Filled Intragastric Balloon System Post Approval Study: Interim Analysis of the first 100 patients with one-year results**

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**Running Title:** Swallowable Gas-Filled Intragastric Balloon Post-Market Approval: 100 Patients

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**What is already known about this subject?**

The Swallowable Gas-Filled Intragastric Balloon system (SGIBS) with lifestyle therapy has demonstrated twice as much weight loss compared with lifestyle therapy alone and a low rate of serious adverse events in a randomized sham controlled study of patients who previously failed lifestyle therapy alone and more weight loss with similar low rate of serious adverse events in a prospectively collected clinical registry series.

**What are the new findings in this manuscript?**

This manuscript describes an interim analysis of the post-market approval study for the SGIBS and evaluates predictors of weight loss success for the SGIBS. Most notably, the number of lifestyle therapy sessions attending positively correlated with weight loss and a history of depression negatively correlated with weight loss at SGIBS removal

**How might your results change the direction of research or the focus of clinical practice?**

The data in this manuscript highlights the importance of lifestyle therapy intensity in maximizing weight loss in a population of patients who have previously not been successful with lifestyle therapy alone. Further research is needed to determine how to improve weight loss outcomes in patients with pre-existing depression prior to SIGBS treatment

**Objective:**To report the predictors of successful weight loss in an interim analysis of the first 100 patients treated in the swallowable gas filled intragastric balloon system (SGIBS) US Post Market Approval Study.

**Methods:** Patients age 22years and older with a body mass index of 30-40 kg/m2 and undergoing treatment with the SIGBS across 13 study sites in the US were eligible. The main outcomes were percent total body weight loss (%TBWL) at balloon removal and predictors of weight loss success at balloon removal.

**Results:** One Hundred patients (age 43.2 ± 10.2, BMI 35.2 ± 3.1 kg/m², female sex 75%) were included in the modified intention to treat analysis (mITT) and n=89 patients were included in the Completer analysis. Weight loss at balloon removal was 10.1% ± 6.2% and 10.7% ± 6.1% TBWL in the mITT and Completer analyses, respectively. The number of lifestyle therapy sessions positively correlated with weight loss at balloon system removal and a history of depression negatively correlated with weight loss at balloon system removal. No serious adverse events occurred.

**Conclusion:** This analysis demonstratesignificant weight loss with the SGIBS and the importance of lifestyle therapy to maximize weight loss. Further research is needed to determine how to improve weight loss outcomes in patients with a history of depression.

**Abbreviations:**Body Mass Index (BMI), Endoscopic Bariatric Therapy (EBT), Percent Excess Weight Loss (%EWL), Percent Total Body Weight Loss (%TBWL), Swallowable Gas-Filled Intragastric Balloon System (SGIBS).

**Introduction**

 Obesity affects 39.6% of adults in the US1. Treatment strategies of lifestyle therapy, weight loss medications, and bariatric surgery have not been sufficient to halt the increase in prevalence of obesity. This may in part be due to low numbers of patients treated with weight loss medications and bariatric surgery, both of which have been demonstrated to achieve more weight loss than lifestyle therapy alone. Several studies suggest only 1-2% of patients who meet criteria are treated with weight loss medications and only 1% of patients who meet criteria for bariatric surgery undergo bariatric surgery each year2-4. There are likely multiple factors contributing to the low numbers of patients treated for obesity, but patient preference is likely a major contributing factor. This supports the need for additional therapies to treat obesity.

 Recently, a new class of therapies, endoscopic bariatric therapies (EBT), has emerged as a treatment option for patients with obesity. These are devices or procedures that are placed or performed endoscopically.One type of EBT is the intragastric balloon, one of which is the Swallowable Gas-Filled Intragastric Balloon System (SGIBS). The SGIBS is comprised of 3 multilayer polymeric balloons, each filled with 250 ccc of a nitrogen mix gas. The balloons are administered deflated and folded within a hard cellulose or gelatin U.S Pharmacopeia – grade capsule and attached to a thin catheter. After the capsule is swallowed, advancement to the stomach is verified with both a navigation system and pressure gauge. The balloon is then inflated and the catheter is ejected from the balloon. This process is repeated for the second and third balloon, all of which are administered separately within 6-12 weeks after administration of the first balloon5,6.

This SGIBS was approved for use in the United States based on the results of a US multi-center randomized sham-controlled trial demonstrating twice as much weight loss with the SGIBS compared with lifestyle therapy alone and a low serious adverse event rate of 0.3%6. This continued safety profile was seen with the US prospective clinical balloon registry, the largest US balloon registry to date, demonstrating a serious adverse event rate of 0.15% and weight loss of 10.0±6.1% TBWL in the indicated patient population with the intended use5.However, no intragastric balloon studies in the US have evaluated factors that are associated with weight loss.A post-market approval study of the SGIBS was started in 2018 with the primary aim of evaluating system performance and safety in clinical practice. The aim of this manuscript is to describe the weight loss and predictors of weight loss success at balloon system removal in the first 100 patients enrolled in the post-market approval study. The primary safety analysis requires the full cohort however; safety information collected to date will also be presented.

**Methods**

Trial Design

 This was a multi-center1-year prospective, single arm, open label study to determine the continued system performance and safety in a commercial setting across 13 sites in the US with first patient enrollment in June 2018. After becoming a commercial patient and passing all screening assessments, patients were enrolled in the post market approval study. The study was approved by each individual study site institutional review board, and written informed consent was obtained from all participants in accordance with the guidelines from the Declaration of Helsinki. The study as registered on clinicaltrials.gov (NCT03570034).

Participants

 Adults 22 years of age and older with a Body Mass Index (BMI) of 30-40 kg/m2 who have previously attempted weight loss using medically supervised or non-medically supervised programs and willing to adhere to treatment guidelines in the instructions for use7. Patients were recruited from clinical practices at each of the 13 study sites who intended to purchase the SGIBS. Inclusion and exclusion criteria were determined during clinical evaluation prior to scheduling the first balloon administration as part of standard of care. Key exclusion criteria included: contraindication for use of the SGIBS per the instructions for use, use of medications or medical devices known to induce weight gain or weight loss within the preceding 6 months, known history of endocrine disorder affecting weight, participation in any clinical study which could affect weight loss within the past year, known history or present condition of structural or functional disorders of the esophagus, life expectancy less than 1 year, or severe medical condition in the opinion of the investigator. Only patients who had completed all pre-balloon administration clinical standard of care evaluations and had presented for first balloon administration were enrolled in the study.

Study Activities Follow-Up Care and Questionnaires

 All activities related to the administration, management, and removal of the SGIBS were conducted in accordance with the device labeling. In addition, each patient had access to both individualized lifestyle therapy sessions and group lifestyle therapysession conducted by a healthcare practitioner with training in nutritional counseling and lifestyle therapy each month. All patients were prescribed proton pump inhibitors as outlined in the instructions for use. Questionnaires including the RAND SF-368 and the Influence of Weight on Quality of Life-Lite9, were administered at baseline, 6-month (removal) and one-year to evaluate components of quality of life with SGIBS treatment. The Rhodes Index for Nausea, Vomiting, and Retching10 was collected at day 1 and day 7 after each balloon administration and at the onset of new nausea, vomiting, or retching.

Outcomes

 The co-primary effectiveness endpoints for evaluation in this manuscript are 1) percent total body weight loss (%TBWL) at balloon removal and 2) predictors of weight loss at balloon removal. Secondary endpoints include: %TBWL at one-year, 5%TBWL Responder Rate defined as the percentage of patients who achieved ≥5% TBWL at removal and the 10% TBWL Responder Rate defined as the percentage of patients who achieved ≥10% TBWL at removal as well as the safety analysis. The weight loss effectiveness metrics for this manuscript include the following populations:

* The modified intention to treat analysis (mITT) cohort includes all subjects who received at least one properly inflated balloon for any duration of time
* The all balloon completeranalysis (Completer) cohort includes all subjects who received at least one balloon with a minimum balloon therapy of 22 weeks duration.
* The durability effectiveness cohort included all subjects followed for at least 48 weeks after the initial balloon and who lost at least 0.1 lbs during balloon therapy.

Calculations

Percent total body weight loss was calculated as:

*%TBWL= (Starting Weight (kg)-Ending Weight (kg))/(Starting Weight (kg)) ×100%*

Percent Excess Weight Loss was calculated as:

*%EWL= (Starting Weight (kg)-Ending Weight (kg))/(Excess Weight (kg)) ×100%*

*Excess Weight (kg)=Starting Weight(kg)-Weight (kg)for a BMI of 25 kg⁄m2*

Statistical Methods

For the post market approval study, study sample size of 200 mITT patients was based on allowing up to 10% attrition rate for a minimum evaluable sample size of 180 patients to obtain 80% power for the study primary safety endpoint (device-procedure related adverse event rate) using a one-sided 0.025 significance level. In this interim analysis, all means listed are reported as mean ± standard deviationand general linear regression analysis was performed to identify predictors of weight loss success (%TBWL at balloon removal).All analyses were conducted on data as entered with no imputations. SAS 9.3 (Cary, NC) software was used to perform all the statistical analyses.

**Results**

Participants

In this analysis of the first consecutiven=100 successfully administered balloon patients, n=109 were enrolled and in n=102 SIGBS therapy was attempted.Seven patients were enrolled, but did not attempt balloon administration and two patients were not able to swallow the SIGBS capsule. All n=100 patients who had at least one balloon successfully administered were included in the mITT analysis. Baseline demographics and characteristics are seen in Table 1. N=89 patients completed at least 22 weeks of therapy with any number of balloons and were included in the Completer analysis (Figure 1). Balloon administration success rates were 98.0%, 99.0%, and 98.9% for the first, second, and third balloon administrations, respectively. Three of these swallow failures did not pass the upper esophageal sphincter and one failed to transit the esophagus. Only 4% of patients had devices removed early due to symptoms. All patients in the mITT analysis had a study duration of at least 48 weeks, but only 49% of patients completed the 48 week time point visit. Of these patients, n=48 were included in the durability effectiveness cohort. The average number of lifestyle therapy sessions attended including both group and individual sessions was 8.5 and 88% of patients had at least 6 lifestyle therapy sessions in the first 6 months of therapy.

Weight Loss Outcomes

 At balloon removal, patients in the mITT cohort achieved 10.1% ± 6.2% TBWL, 38.1% ± 27.4 Percent Excess Weight Loss (%EWL), and 3.5 ± 2.1 kg/m2 BMI change; while patients in the Completer cohort achieved 10.7% ± 6.1% TBWL, 40.0% ± 27.7% EWL, and 3.7 ± 2.1 BMI change.In patients who completed the 48 weeks visit, the durability effectiveness cohort achieved 9.2% ± 7.3% TBWL, 35.0% ± 28.9% EWL, and 3.2 ± 2.6 BMI change. The 5% TBWL Responder Rate for the mITT cohort was 81.0% and for the Completer cohort was 84.3%. The 10% TBWL Responder Rate for the mITT cohort was 49.0% and for the Completer cohort was 51.7%%.

Predictors of Weight Loss

 General linear regression was performed with the mITT cohort including all 100 patients who were successfully treated with the SIGBS. The summary of predictors of weight loss can be seen in Table 2. The only positive predictor of weight loss was the number of behavioral counseling sessions attended in the first 6 months. Only 2 patients received exactly one balloon, so although the β for multiple balloons was high at 5.76, it was not statistically significant (p=0.1771) due to the small sample size comparison. The only positive predictor of weight loss was number of behavior counseling sessions attended (β 0.65, p=0.0010) while history of depression at the time of enrollment was a negative predictor of weight loss (β -5.78, p=0.0005)

Safety

 Data collection is ongoing for serious adverse events in the entire population of the post-market approval study. No serious adverse events related to the device or procedure occurred in the first n=100 patients, and at the time of writing of this manuscript, no serious adverse events related to the device or procedure were seen in any patient enrolled in the study. However further analysis cannot be performed at this time. Non-serious adverse events occurred in 86% of patients with 468 events. The most common device or procedure non-serious adverse events in patients included nausea (79%), retching (49%), vomiting (40%), abdominal pain (23%), dyspepsia defined as dyspepsia and reflux (8%) (Table 2). None of the non-serious adverse events were rated as severe, and 91.2% were rated asymptomatic or mild. Of note, individual events of nausea, retching, or vomiting could be reported on both the Rhodes Index and directly to the study team during visits, leading to two reports of one incidence. Therefore, an unknown number of individual events were counted twice, raising the overall number of adverse events. However, the percentage of patients who experienced any adverse event was not affected. One deflation occurred out of 284 balloons placed, but passed out of the GI tract without sequela and was diagnosed upon scheduled removal when only two balloons were present in the stomach of a patient who had three balloons administered.

**Discussion**

In this interim analysis of the SGIBS post-market approval study, an open-label single arm study, we found that weight loss was consistent with weight loss seen in patients from the SGIBS prospective patient registry, the largest known US registry of an endoscopic bariatric therapy to date5. In addition, the number of behavioral counselling sessions attended was a positive predictor of weight loss success and a history of depression was a negative predictor. The high safety profile of the SGIBS was again demonstrated with no device or procedure related serious adverse events reported in the first 100 patients or any patient currently enrolled, consistent with both the US registry and the US pivotal trial5,6. The current analysis also includes 1 year weight loss maintenance data, which demonstrates a high percentage of weight loss maintenance, consistent with the US pivotal trial6.

The weight loss achieved in this open label evaluation of the SIGBS is higher that the weight loss achieved in the US pivotal trial which was a randomized sham controlled trial6. Lower weight loss in patients who are blinded to their treatment status has been a consistent finding in endoscopic bariatric therapies. In a direct comparison of open label to randomized patients in a randomized sham-controlled study with an unblinded lead-in group, patients in the lead-in group achieved 40% more weight than patients in the randomized active group who were unaware of their study assignment 11. In concordance with that data, weight loss in both clinical case series of IGBs that underwent randomized sham controlled studies in the US also demonstrated roughly 40-50% more weight loss in the open label clinical case series than the US multi-center randomized sham-controlled trials 5,6,12,13.

The predictors of success for weight loss seen in this trial are similar to that seen in a retrospective registry series of a single fluid filled balloon in US adults, which demonstrated similar β for follow-up visits between 0 and 6 months as this study (0.4, p=0.024), but did not find a significant correlation with depression (β -1.47, p=0.17)14. Our finding of number of lifestyle therapy session as a predictor of weight loss is also consistent with data from lifestyle therapy or diet studies15-17 and medications18,19. Depression has been shown to be more prevalent among patients with obesity20, but a recent meta-analysis did not find an association between pre-operative depression and post-operative weight loss in a bariatric surgery population21. It is unclear why depression was a strong negative predictor of weight loss in this study, but suggests that integration of depression and obesity treatment in patients with baseline depression may improve weight loss with the SIGBS as seen in with lifestyle therapy alone22.

The non-serious adverse events that occurred in this interim analysis of the SIBGS were similar to the non-serious adverse events in the US SIGBS pivotal trial in terms of both rates and severity. In the US SIGBS pivotal trial, 90.8% of patients experienced at least one non-serious adverse event, 82.2% were rated mild and only 0.5% were rated severe6. In this analysis, 86% percent of patients experienced at least one non-serious adverse and 91.2% of them were rated asymptomatic or mild and none were rated severe. These rates are significantly higher than the rates of non-serious adverse events reported in the prospective clinical registry, in which only 14.2% of patients reported a non-serious adverse event5. The differences in these rates are likely due to the intensive methods for adverse event assessment in the US pivotal trial and the present analysis. In the US pivotal trial for the SIGBS, patients were called within 24 hours of balloon administration and were questioned at each 3 week follow-up for adverse events while patients in the present study filled out a Rhodes Index of Nausea and Vomiting on day 1 and 7 after each balloon administration and at any time if symptoms developed. This is in comparison to the clinical prospective registry where patients were not directly asked at specified time points for adverse events, but rather patients reported adverse events as they occurred or needed treatment. Since the vast majority of the non-serious adverse events in the US pivotal trial and this analysis were rated as mild or asymptomatic, by definition they did not require additional treatment and would likely not have been communicated in clinical practice. This highlights the general high tolerability of the SIGBS. Although not reported as an adverse event, one balloon deflation occurred that was noted when the third balloon was not present at the time of scheduled removal. This low rate of deflation without sequela is consistent with both the US pivotal trial and the US prospective registry 5,6.

No serious adverse events occurred in the patients included in this analysis or in any patient currently enrolled in the post market approval study. This is consistent with the rates of serious adverse events reported in the US pivotal trial (0.3%) and the US prospective clinical registry (0.15%). This is in comparison to the fluid filled IGB’s which have recently been approved and marketed in the US (the dual fluid filled intragastric balloon is no longer commercially available) which demonstrated serious adverse event rates of 7.5-10%13,23.

There are several limitations to this study. First, the data we present are from an interim analysis of the SIGBS Post Market Approval study and do not include the entire study population. Due to the COVID pandemic, the decision was made to proceed with publishing the interim results of the study, which have already been submitted to the Food and Drug Administration. However, more than 100 patients have enrolled in the study and no serious adverse events have occurred in any subject currently enrolled in the study at the time of submission of this manuscript. Moreover, the weight loss data seen in the first 100 patients is similar to the large prospective registry series, which suggests that additional subjects will not have a significant effect on the weight loss findings. Second, the majority of the patients in this study are women. This is common among both the US pivotal trials as well as the registry series of endoscopic bariatric therapies and does represent a typical clinical population5,6,11-14,23,24. Third, laboratory evaluation of cardiometabolic diseases was not performed in this study. The weight loss achieved both at 6 and 12 months is associated with cardiometabolic benefits25-27, but since laboratory values were not obtained, this could not be verified in our study.

**Conclusions**

In conclusion, the interim analysis of the SIGBS post market approval study demonstrates clinically significant weight loss and low risk consistent with the previously published largest prospective endoscopic bariatric therapy device registry in the US and highlights the importance of follow-up lifestyle therapy sessions for weight loss success. The negative predictor of history of depression on weight loss suggests that additional therapy for depression may help to increase weight loss in patients with a history of depression. These data support the use of the SIGBS as an effective and safe treatment for obesity in conjunction with lifestyle therapy, but further research is needed to determine methods for improving weight loss for patients with depression who are treated with the SIGBS.

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**Figure 1**. CONSORT Flow Diagram

**Table 1.** Table 1. Baseline patient demographics and characteristics, n=100. BMI: Body Mass Index, kg/m2: kilograms per meter squared, in: inches, lbs: pounds, SD: Standard Deviation

**Table 2.** Device or Procedure Related non-serious adverse events reported in n=100 patients

Table 1. Baseline patient demographics and characteristics, n=100

| **Baseline** | **Mean ± SD(Minimum, Maximum)Or Patients (% of Total)** |
| --- | --- |
| Age (years) | 43.2 ± 10.2  [21.0, 67.0] |
| Female | 75 (75.0%) |
| Not Hispanic or Latino | 77 (77.0%) |
| White | 87 (87.0%) |
| Height (in) | 66.1 ± 4.3 [57.5, 80.0] |
| Starting weight (lbs) | 220.4 ± 38.3[157.0, 331.0] |
| Starting BMI (kg/m²) | 35.2 ± 3.1 [30.1, 41.8] |
| Starting excess weight (lbs) | 64.3 ± 22.6 [29.6, 122.9] |

BMI: Body Mass Index, kg/m2: kilograms per meter squared, in: inches, lbs: pounds, SD: Standard Deviation

Table 2. Predictors of weight loss at balloon removal

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **β** | **p-value** | **95% Confidence limits** |
| Gender (Female) | 1.64 | 0.2286 | -1.05 | 4.32 |
| Age (years) | 0.05 | 0.3451 | -0.06 | 0.16 |
| Baseline BMI | -0.16 | 0.3928 | -0.53 | 0.21 |
| Multiple Balloon (yes) | 5.76 | 0.1771 | -2.65 | 14.16 |
| GERD (yes) | -0.20 | 0.9004 | -3.32 | 2.92 |
| Depression (yes) | -5.78 | 0.0005 | -8.95 | -2.61 |
| Number of Counseling Sessions | 0.65 | 0.0010 | 0.27 | 1.03 |

BMI: Body Mass Index, kg/m2: kilograms per meter squared, GERD: Gastroesophageal Reflux Disease

| **Adverse Events** | **Severity (% of Events)** |
| --- | --- |
| **Type** | **Patients(% of Total)** | **Events** | **Asymptomatic** | **Mild** | **Moderate** | **Severe** |
| Nausea | 79 (79.0%) | 224 | 0 (0.0%) | 211 (94.2%) | 13 (5.8%) | 0 (0.0%) |
| Retching | 49 (49.0%) | 103 | 0 (0.0%) | 94 (91.3%) | 9 (8.7%) | 0 (0.0%) |
| Vomiting | 40 (40.0%) | 77 | 0 (0.0%) | 70 (90.9%) | 7 (9.1%) | 0 (0.0%) |
| Abdominal pain | 23 (23.0%) | 32 | 0 (0.0%) | 30 (93.8%) | 2 (6.3%) | 0 (0.0%) |
| Dyspepsia | 8 (8.0%) | 10 | 0 (0.0%) | 4 (40.0%) | 6 (60.0%) | 0 (0.0%) |
| Constipation | 4 (4.0%) | 4 | 0 (0.0%) | 4 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Gastric irritation | 3 (3.0%) | 3 | 1 (33.3%) | 2 (66.7%) | 0 (0.0%) | 0 (0.0%) |
| Diarrhea | 2 (2.0%) | 3 | 0 (0.0%) | 3 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Epigastric pain | 2 (2.0%) | 2 | 0 (0.0%) | 1 (50.0%) | 1 (50.0%) | 0 (0.0%) |
| Difficulty in sleeping | 2 (2.0%) | 2 | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Eructation | 2 (2.0%) | 2 | 0 (0.0%) | 2 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Intermittent gastric outlet obstruction  | 1 (1.0%) | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Gastric ulcer | 1 (1.0%) | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Neck pain | 1 (1.0%) | 1 | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) |
| Anxiety | 1 (1.0%) | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Gastric abrasion/bleeding | 1 (1.0%) | 1 | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Esophageal abrasion/bleeding | 1 (1.0%) | 1 | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **ALL** | **86 (86.0%)** | **468** | **2 (0.4%)** | **425 (90.8%)** | **41 (8.8%)** | **0 (0.0%)** |

**Table 2**. Device or Procedure Related non-serious adverse events reported in n=100 patients

