

ORIGINAL ARTICLE

Intragastric balloon as an adjunct to lifestyle intervention: a randomized controlled trial

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BACKGROUND/OBJECTIVES: This trial evaluated the safety and effectiveness of the Orbera Intragastric Balloon as an adjunct to lifestyle intervention.

SUBJECTS/METHODS: In this multicenter, randomized, open-label clinical trial, 255 adults with a body mass index of 30–40 kg m⁻² were treated and outcomes were assessed up to 12 months. Participants were randomized to endoscopic placement of an intragastric balloon plus lifestyle or lifestyle intervention alone. Balloons were removed at 6 months and lifestyle intervention continued for both groups through 12 months. At 9 months, coprimary end points were two measures of weight loss.

RESULTS: At 6 months, weight loss was –3.3% of total body weight (–3.2 kg) in the lifestyle arm vs –10.2% (–9.9 kg) in the balloon plus lifestyle arm ($P < 0.001$); at 9 months (3 months postballoon removal), weight loss was –3.4% (–3.2 kg) vs –9.1% (–8.8 kg, $P \leq 0.001$); and at 12 months, –3.1% (–2.9 kg) vs –7.6% (–7.4 kg, $P \leq 0.001$). For the primary end points, at 9 months, mean percent loss of weight in excess of ideal body weight (s.d.) at 9 months was 26.5% (20.7) ($P = 0.32$) and 9.7% (15.1) in the balloon and control groups, respectively. Also, 45.6% (36.7, 54.8) of the subjects randomized to the balloon achieved at least 15% loss of weight in excess of ideal body weight greater than the control group ($P < 0.001$). The majority of balloon subjects experienced adverse events; 86.9% nausea, 75.6% vomiting, 57.5% abdominal pain and 18.8% had their device removed before 6 months because of an adverse event or subject request. Five subjects (3.1%) in the balloon group had a gastric abnormality at the time of device removal, and no ulcers were found.

CONCLUSIONS AND RELEVANCE: Intragastric balloon achieved greater short-term weight loss at 3 and 6 months postballoon removal than lifestyle intervention alone. Adverse gastrointestinal events were common.

International Journal of Obesity (2017) 41, 427–433; doi:10.1038/ijo.2016.229

INTRODUCTION

Obesity affects an estimated 78 million or 36% of adults in the United States.¹ Obesity raises the risk of morbidity and mortality from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, sleep apnea and other respiratory problems, as well as some cancers.^{2,3} This population is also at risk for many other debilitating conditions including musculoskeletal disease, liver disease and impairment of fertility.⁴ Individuals with obesity may also suffer from social stigmatization and discrimination.⁵ For many of the obesity-related comorbid conditions, a reduction in body mass index (BMI) can help to improve symptoms or resolve the problem.⁶ Although bariatric surgery is effective for weight loss, many people cannot or do not wish to undergo a surgical procedure.^{7,8} In addition, pharmaceutical alternatives are limited and may not be suitable for or accepted by some people. There is a need for additional alternatives to help treat obesity.

The Orbera intragastric balloon (IGB) has been used outside of the United States for over 17 years and has been distributed to over 200 000 people in more than 80 countries and serves as an intermediate option between lifestyle change (diet and exercise) and bariatric surgery. The IGB may act by partially filling the stomach, acting as an artificial bezoar, to augment weight loss by inducing early satiety and perhaps also by slowing gastric emptying. It is made of a soft, smooth silicone elastomer that

expands to a spherical shape when filled with saline and is placed in the stomach where it moves freely. A detachable catheter fills the IGB under endoscopic observation. The IGB is designed to dwell in the stomach for a maximum of 6 months after which time the device is removed and lifestyle changes would continue. The primary aims of this trial were to study the safety and effectiveness of the IGB for weight loss among individuals in the United States with class I and II obesity (BMI 30–40 kg m⁻²).

MATERIALS AND METHODS

Study design

This was a sponsor-initiated, multicenter, prospective, randomized, open-label, comparative, Pivotal Study, conducted under a Food and Drug Administration Investigational Device Exemption. Participating institutional review boards approved the protocol, and written informed consent was obtained from all subjects. The clinical trial was registered in the National Institutes of Health website: www.clinicaltrials.gov, entitled, 'Randomized, Multicenter Study to Evaluate the Safety and Effectiveness of the BIB IGB System as an Adjunct to a Behavioral Modification Program, in Comparison with a Behavioral Modification Program Alone in the Weight Management of Obese Subjects' and referred to as the 'BIB' or 'IB-005' study. The study was designed, funded and conducted by Allergan Medical (Santa Barbara, CA, USA), which was acquired by Apollo Endosurgery who renamed the BIB IGB System the Orbera System. The first author wrote the paper with critical editorial input from the coauthors. The authors decided to publish

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Received 9 June 2016; revised 31 August 2016; accepted 20 October 2016; accepted article preview online 23 December 2016; advance online publication, 24 January 2017

the paper and vouch for the completeness and accuracy of the data and the data analyses.

Intervention

There were 15 investigational sites in the United States that participated in the trial. Eligible subjects were adults, aged 18–65 years, with obesity and a body mass index (BMI) of ≥ 30 and $\leq 40 \text{ kg m}^{-2}$, a history of obesity for at least 2 years with failed conservative weight loss attempts, such as supervised diet, exercise, and behavioral modification programs. Race was self-reported. Potential subjects with a history of foregut or gastrointestinal (GI) surgery (except uncomplicated cholecystectomy or appendectomy), GI obstruction, adhesive peritonitis or clinically significant hiatal hernia were excluded (Supplementary Appendix 1). Also excluded were those with a history or symptoms of esophageal or GI motility disorder, a patulous pyloric channel, symptoms of delayed gastric emptying, a history of inflammatory bowel disease or a positive test for *Helicobacter pylori* at screening. Each investigator was mentored while placing and removing IGB devices in up to five run-in subjects before placing in study subjects. Run-in subjects met the same eligibility criteria and followed the same visit schedule and lifestyle intervention program as study subjects and were included in the safety reporting. Study subjects randomized to the IGB group underwent placement of the device followed by removal at 6 months in addition to a lifestyle intervention program. Both study groups participated in a 12-month lifestyle program that incorporated the following elements: a low calorie (1000–1500 calories per day) diet, daily food and exercise diary, encouragement to exercise and emphasis on behavioral change during a total of 21 visits (9 visits in months 1–6, 12 visits in months 7–12).

Randomization was performed using an interactive voice response system and subjects were assigned in a 1:1 ratio to either IGB plus lifestyle or lifestyle-alone (control group). The IGB was placed under deep sedation or general anesthesia, through the esophagus and into the stomach under endoscopic observation. Using an attached removable fill tube, the device was filled with sterile saline to a volume between 500 and 600 cm^3 . The balloon was deployed freely to move within the stomach and remained in place for 6 months. Removal was performed endoscopically, under anesthesia, by puncturing the balloon with a needle cannula, withdrawing the saline, then grasping and extracting the collapsed device through the mouth. Medications were used optionally after IGB placement to prevent or lessen the expected common side effects of nausea and vomiting in the early postprocedure period.

Study outcomes

There were two coprimary effectiveness end points evaluated at 9 months after treatment initiation, which was 3 months after the IGB was removed. The first primary end point was to demonstrate that the mean percent excess weight loss (%EWL) (using the 1983 Metropolitan Life Tables (using the mid-point of the medium frame) to determine ideal body weight (IBW)) was significantly $> 25\%$ EWL. The second primary end point was the percentage of IGB subjects with significantly greater weight loss than the control group at 9 months. Significantly greater weight loss was defined as $\geq 15\%$ EWL (using the 1983 Metropolitan Life Tables (using the mid-point of the medium frame to determine IBW) over the mean %EWL of the control group). Effectiveness analyses were also conducted at 6, 9 and 12 months in pounds and percent total body weight loss. Secondary end points were changes comorbid conditions and quality of life, including depression, at 9 months. Changes in severity of type 2 diabetes, hypertension and dyslipidemia were based on the predefined criteria that included laboratory values and vital signs (Supplementary Appendix 2). Quality of life measures were the SF-36, IWQOL-Lite and the Beck Depression Inventory II. Safety was assessed in both run-in and study subjects as the incidence and severity of adverse events (AEs) related to treatment.

Statistical analysis

A sample size calculation was completed using a two-group continuity corrected χ^2 test with a 0.025 two-sided significance level to have 80% power to test the hypothesis related to one of the coprimary end points: that at least 30% of the IGB group will achieve success (defined as 15% greater EWL over the mean %EWL of the control group) with sample sizes of 160 and 160, respectively (a total sample size of 320). The primary analysis population for this study was the modified intention-to-treat population, which comprised all randomized subjects who underwent an

intervention (balloon=having device placement; control=commencing lifestyle program). Only those who did not undergo an intervention were excluded from the modified intention-to-treat population, as was stated in the initial analysis plan. Missing values for the coprimary end points were imputed using the last observation carried forward method, also according to the initial analysis plan. Sensitivity analyses for the coprimary end points were also analyzed using baseline observation carried forward and using multiple imputation methods and are presented in the figures in the results. Coprimary end point one was assessed using a Wilcoxon's sign-rank, one-sample test. Coprimary end point two was assessed with an exact binomial test. Estimates of and comparisons between groups in percent total body weight loss and weight loss (in kilograms) were conducted using a mixed-effects model including treatment group, study week and treatment group-by-study week interaction assuming random intercepts. Differences between treatment groups in responder rates (risk difference and 95% confidence intervals) at each time point were conducted using a χ^2 test. Difference between treatment groups for the rates of comorbidities were analyzed by a χ^2 test at 9 months. Treatment comparisons for the additional secondary end points of each SF-36 domain, IWQOL-Total and Beck Depression Inventory total were analyzed using a repeated-measures model, adjusting for baseline values. A Bonferroni adjustment was applied to the 13 secondary end points at month 9. An exploratory analysis included a linear regression model to assess potential baseline predictors of % total body weight loss at 12 months.

RESULTS

Study participants

Enrollment began on 20 June 2008 and last follow-up was on 8 June 2011. A total of 448 subjects were enrolled, of which 131 failed screening procedures, most commonly (22%) due to *H. pylori* infection, so that 317 subjects were randomized; 44 were run-in subjects, 137 subjects to IGB and 136 subjects to the control group. Therefore, the total planned sample size was enrolled but not all were treated. A total of 125 of the 137 IGB subjects underwent device placement and 130 of 136 control subjects underwent treatment and have data included for the analyses of primary and secondary end points. Safety was assessed in both run-in and study subjects for the IGB ($n = 35 + 125 = 160$). Follow-up at 6 months (IGB removal time) was 94% overall (IGB 95%, control 93%), at 9 months was 92% overall (IGB 94%, control 90%) and at 12 months was 75% overall (IGB 78%, control 72%) (Figure 1). Thirty of the 160 subjects (18.8%) in the device group had the IGB removed before month 6, and these are detailed in the AEs.

The study groups were comparable at baseline (Table 1). The mean age was 39–40 years, 90% of were female, and just over 80% Caucasian. At baseline, the mean weight was 98 kg, BMI was 35 kg m^{-2} and the average excess weight using the mid-point of the medium frame on the 1983 Metropolitan Life tables to determine IBW was 36 kg. Over half of the subjects in both groups had a history of obesity for 10 years or more. Baseline prevalence rates of type 2 diabetes, hypertension and dyslipidemia were 7%, 26% and 39%, respectively, in the IGB group and 6%, 28% and 30%, respectively, in the control groups. All IGB-treated subjects had the device placed successfully and filled to the recommended fill volume of $550 \pm 50 \text{ cm}^3$ with mean duration of placement (defined as time endoscope placed to removal) of 12.3 min (range, 5–43). There were no early device failures (deflations). All subjects had successful removal of the device and the removal procedure was 19.5 min (range, 6–60).

Weight change and primary end points

At 6 months, weight loss was -3.3% of total body weight (-3.2 kg) in the lifestyle modification arm vs -10.2% (-9.9 kg) in the balloon plus lifestyle intervention arm ($P < 0.001$); at 9 months (3 months postballoon removal), weight loss was -3.4% (-3.2 kg) vs -9.1% (-8.8 kg , $P \leq 0.001$); and at 12 months, -3.1% (-2.9 kgs) vs -7.6% (-7.4 kgs , $P \leq 0.001$) (Figure 2 and Supplementary Table 1). For the

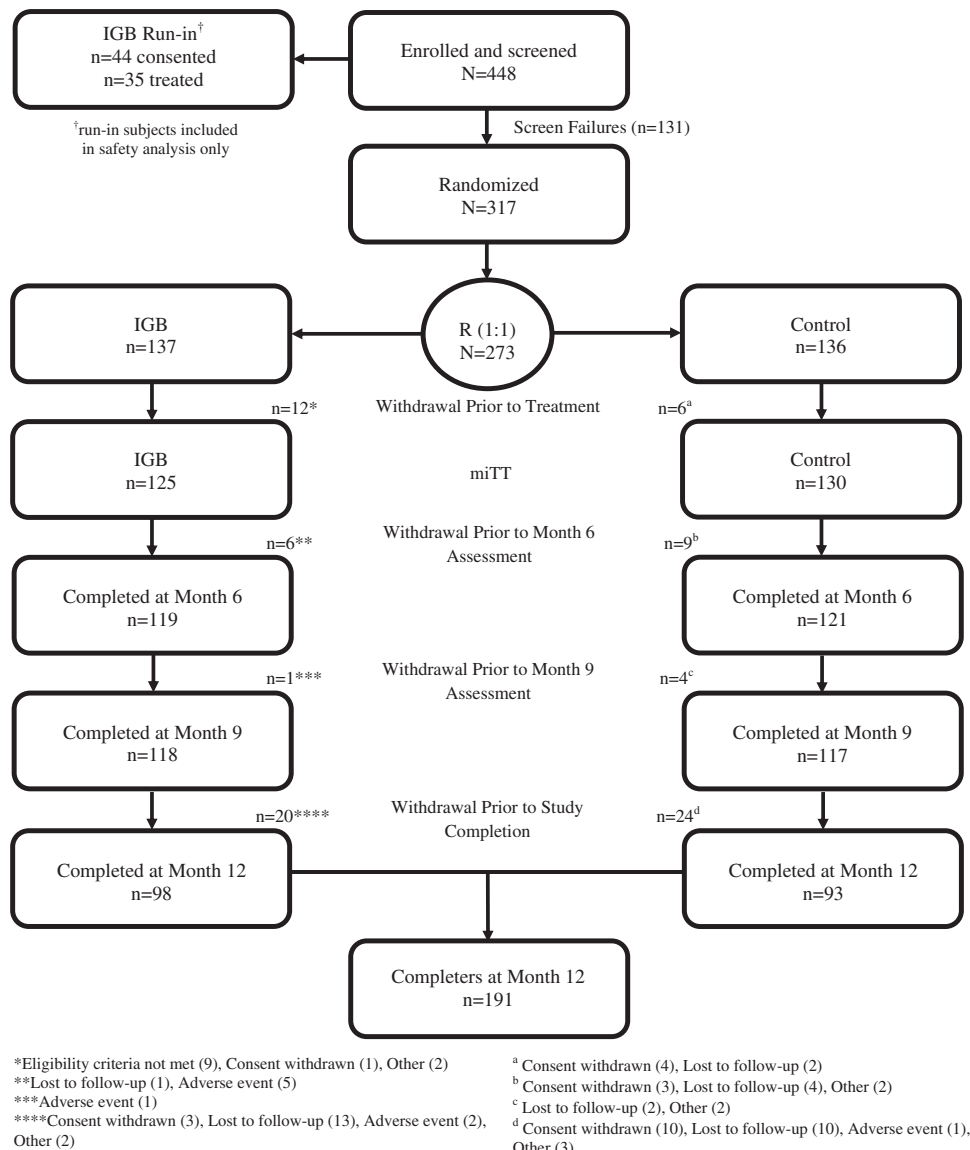


Figure 1. Consort diagram.

coprimary end points, at 9 months follow-up, IGB-treated subjects had a mean %EWL (using the 1983 Metropolitan Life tables to determine IBW) of 26.5% (22.9–30.2, $P = 0.32$) where the target was 25% EWL. The mean differences in %EWL and in total body weight loss between IGB and control are shown in Supplementary Tables 2a and b. For the second coprimary end point, 45.6% (36.7–54.8, $P < 0.001$) of IGB-treated subjects achieved at least 15% EWL over the mean of the control group (Figure 3). Sensitivity analyses for the two primary end points are shown in Figure 3 and the final results using multiple imputation are the same as those using last observation carried forward; one of two weight loss coprimary end points were met. When using baseline observation carried forward for analyses, neither coprimary end point was met. Response rates at the time of device removal (6 months), 46% of the IGB and 12% of the control group had $\geq 10\%$ total body weight loss ($P < 0.001$). At 9 months, 41% of IGB and 14% of the control group had $\geq 10\%$ total body weight loss ($P < 0.001$), and at 12 months, 6 months after device removal, 32% of IGB subjects and 16% of the control group achieved $\geq 10\%$ total body weight loss ($P = 0.003$). Also at 12 months, 60% of the IGB and 30% of the control group had 5% total body weight loss ($P < 0.001$) (Supplementary Table 3).

An exploratory analysis assessed potential baseline predictors of % total body weight loss at 12 months. Of the covariates assessed (sex, age, BMI group (30–35, 36–40), race, years of obesity, diabetes status at baseline, baseline %EWL and % total body weight loss at 3 months), % total body weight loss at 3 months was predictive of weight loss at 12 months ($\beta = 1.23$, $P < 0.001$).

Secondary end points

The IGB intervention was not associated with significant improvements at 9 months in type 2 diabetes, hypertension, or dyslipidemia compared with the lifestyle program alone (Supplementary Table 4). Neither group was highly enriched with comorbid conditions, specifically type 2 diabetes, where the baseline prevalence was 7 and 6% in IGB and control groups, respectively. There were significant differences between groups, in favor of the balloon, in 6 of 8 the SF-36 domains (Supplementary Figure 1) and the IWQOL total score (Supplementary Table 5), at 9 months. There were no significant differences in depression at 9 months between balloon and lifestyle groups (Supplementary Table 5).

Table 1. Baseline characteristics^a

Demographics	IGB, N = 125, n (%)	Control, N = 130, n (%)
Gender		
Female	112 (89.6)	117 (90.0)
Male	13 (10.4)	13 (10.0)
Age (± s.d.)	38.7 (9.37)	40.8 (9.61)
Race		
Caucasian	101 (80.8)	106 (81.5)
Hispanic	9 (7.2)	7 (5.4)
Black (not of Hispanic origin)	14 (11.2)	15 (11.5)
Asian	0 (0)	0 (0)
Other	1 (0.8)	2 (1.5)
Weight (kg) (± s.d.)	98 ± 15	98 ± 12
Excess weight, MetLife (lbs) (± s.d.)	36 ± 11	36 ± 9
BMI (kg m⁻²)		
< 30	2 (1.6)	1 (0.8)
≥ 30 and < 35	63 (50.4)	57 (43.8)
≥ 35 and ≤ 40	56 (44.8)	70 (53.8)
> 40	4 (3.2)	2 (1.5)
Number of years obese		
< 10	55 (44.0)	48 (36.9)
≥ 10	70 (56.0)	82 (63.1)
Comorbid conditions		
Type 2 diabetes	9 (7)	8 (6)
Hypertension	33 (26)	37 (28)
Dyslipidemia	49 (39)	39 (30)

Abbreviations: BMI, body mass index; IGB, intragastric balloon. ^aThere were no statistically significant differences between treatment groups.

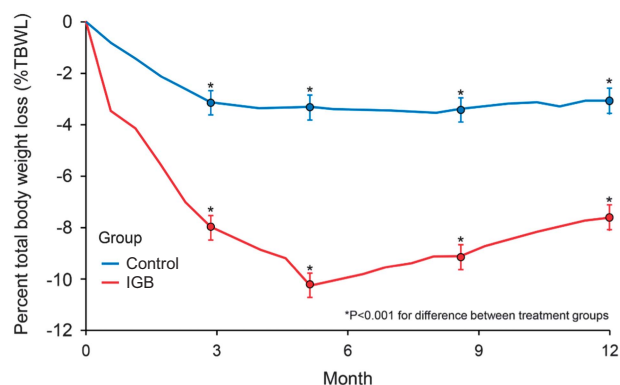
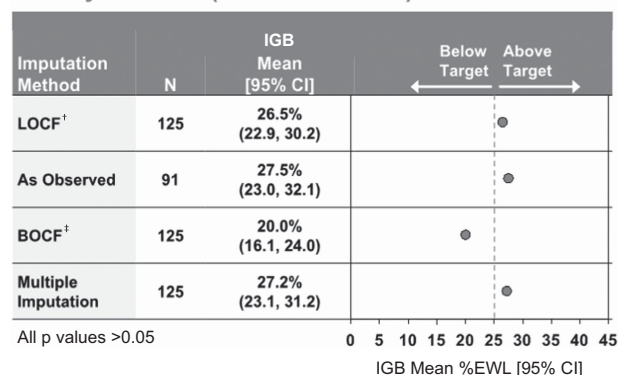


Figure 2. Percent total body weight loss by treatment group. (mITT population using LOCF (last observation carried forward) for missing data values).

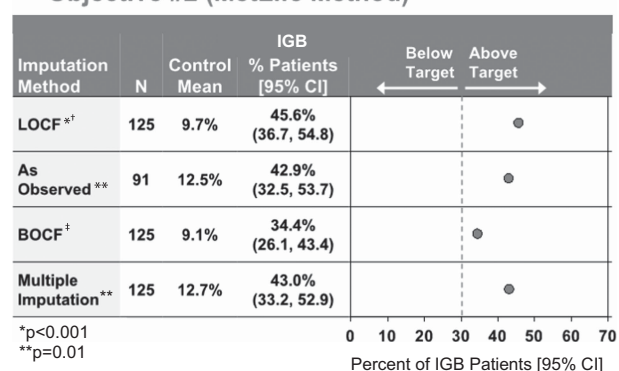
AEs and medications for side effects

Sixteen (10%) IGB subjects had 17 device- or procedure-related serious AEs (SAEs), and 8 (6.1%) control subjects reported SAEs. The most common device-related SAE was device intolerance, resulting in early removal of the device in 8 subjects. A total of thirty of the 160 subjects (18.8%) in the device group had the IGB removed before month 6 because of an AE ($n=15$, 8 due to SAE of device intolerance, almost all others (7) did not meet the definition of an SAE and were due to abdominal pain, reflux, nausea, vomiting) or subject request ($n=15$). Other IGB-related SAEs included two cases of severe dehydration, one gastric outlet obstruction, one gastric perforation with sepsis, one aspiration pneumonia, one severe abdominal cramping, one laryngospasm

Sensitivity Analyses: Primary Effectiveness Objective #1 (MetLife Method)



Sensitivity Analyses: Primary Effectiveness Objective #2 (MetLife Method)



[†] LOCF = last observation carried forward

[‡] BOCF = baseline observation carried forward

Figure 3. Primary effectiveness end points.

during placement and two procedure-related esophageal mucosal injuries (Supplementary Appendix 3). Each of these subjects recovered. There were 810 device-related AEs occurring in 157 of 160 (98.1%) of all the IGB subjects, and 429 AEs occurring in 92 of 130 (70.8%) control subjects experienced an AE (Tables 2a and b). The effect estimates to compare the AE rates and the use of any medication between groups are shown in Supplementary Table 6, confirming that both AEs (especially, GI events) and any medication use were more common in the IGB group. Most of the IGB AEs were mild (59.4%) to moderate (35.6%) in severity and the majority because of GI distress (Table 2a). Included in the AEs were those found at device removal: five subjects had six gastric findings (one infection, one outlet obstruction, one perforation, three gastritis). The majority (91.9%) of IGB and few (6.2%) of control subjects used at least one medication from the classes: antiemetics, anxiolytics, antispasmodic drugs including anticholinergics, proton pump inhibitors, and steroids (Supplementary Table 7).

DISCUSSION

These results demonstrate that the Orbera IGB System was more effective than a lifestyle modification alone in achieving modestly greater short-term weight loss. At 9 months (3 months post-balloon removal), the balloon group had a mean of 5.6 kg (5.7% total body weight) more weight loss than the lifestyle-alone group; at 12 months, the difference was 4.5 kg (4.5% total body weight). Subjects in this study were not followed beyond 6 months after balloon removal (longer than 12 months) to assess whether this difference was maintained over a longer period of time. The

Table 2a. Device-related AEs with frequency $\geq 1\%$ IGB group ($N = 160$)

Event	Total, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
At least one device-related AE	157 (98.1%)	95 (59.4%)	57 (35.6%)	5 (3.1%)
Nausea	139 (86.9%)	73 (45.6%)	59 (36.9%)	7 (4.4%)
Vomiting	121 (75.6%)	54 (33.8%)	61 (38.1%)	6 (3.8%)
Abdominal pain	92 (57.5%)	44 (27.5%)	43 (26.9%)	5 (3.1%)
Gastroesophageal reflux disease	48 (30.0%)	31 (19.4%)	12 (7.5%)	5 (3.1%)
Eructation	39 (24.4%)	35 (21.9%)	4 (2.5%)	0 (0.0%)
Dyspepsia	34 (21.3%)	24 (15.0%)	8 (5.0%)	2 (1.3%)
Constipation	32 (20.0%)	29 (18.1%)	3 (1.9%)	0 (0.0%)
Abdominal pain upper	29 (18.1%)	18 (11.3%)	11 (6.9%)	0 (0.0%)
Abdominal distension	28 (17.5%)	24 (15.0%)	3 (1.9%)	1 (0.6%)
Dehydration	23 (14.4%)	9 (5.6%)	11 (6.9%)	3 (1.9%)
Diarrhea	21 (13.1%)	15 (9.4%)	6 (3.8%)	0 (0.0%)
Flatulence	18 (11.3%)	14 (8.8%)	4 (2.5%)	0 (0.0%)
Impaired gastric emptying	14 (8.8%)	13 (8.1%)	1 (0.6%)	0 (0.0%)
Abdominal discomfort	10 (6.3%)	9 (5.6%)	1 (0.6%)	0 (0.0%)
Asthenia	8 (5.0%)	3 (1.9%)	4 (2.5%)	1 (0.6%)
Postprocedural pain	8 (5.0%)	7 (4.4%)	1 (0.6%)	0 (0.0%)
Headache	8 (5.0%)	6 (3.8%)	2 (1.3%)	0 (0.0%)
Fatigue	7 (4.4%)	5 (3.1%)	2 (1.3%)	0 (0.0%)
Halitosis	6 (3.8%)	6 (3.8%)	0 (0.0%)	0 (0.0%)
Abdominal rigidity	5 (3.1%)	4 (2.5%)	1 (0.6%)	0 (0.0%)
Gastrointestinal pain	5 (3.1%)	2 (1.3%)	3 (1.9%)	0 (0.0%)
Vitamin B1 decreased	5 (3.1%)	3 (1.9%)	2 (1.3%)	0 (0.0%)
Pharyngolaryngeal pain	5 (3.1%)	5 (3.1%)	0 (0.0%)	0 (0.0%)
Esophagitis	4 (2.5%)	3 (1.9%)	1 (0.6%)	0 (0.0%)
Hiccups	4 (2.5%)	4 (2.5%)	0 (0.0%)	0 (0.0%)
Gastritis	3 (1.9%)	2 (1.3%)	1 (0.6%)	0 (0.0%)
Anorexia	3 (1.9%)	2 (1.3%)	1 (0.6%)	0 (0.0%)
Anemia	2 (1.3%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Epigastric discomfort	2 (1.3%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Fecal incontinence	2 (1.3%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Migraine	2 (1.3%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Alopecia	2 (1.3%)	2 (1.3%)	0 (0.0%)	0 (0.0%)

Abbreviations: AE, adverse events; IGB, intragastric balloon.

majority of subjects in the balloon group reported GI AEs, many were treated with medications to control symptoms and just under 20% had the device removed early. The balloon treatment was not associated with significant improvements in the small group with diabetes (7% balloon; 6% control), hypertension, dyslipidemia or depression, but was associated with improved quality of life compared with lifestyle modification alone.

Treatment with intensive lifestyle modification is associated with reductions in weight of 4–7% total body weight loss.^{9,10} There is a critical need for additional tools to augment weight loss above what can be accomplished with lifestyle intervention alone. The pharmacological approaches to treat obesity may be associated with unfavorable side effects but do increase average weight loss by 3 to 9% compared with lifestyle therapy.¹¹ The IGB treatment option can be added to the set of adjunctive clinical tools available to help augment the results of lifestyle treatment alone in people with class I and II obesity. In this trial, it appears that the only predictor of 12-month weight loss in the balloon group was the amount of weight lost by the first 3 months of balloon treatment. Thus, more research is needed to better understand the individual predictors of treatment response. Bariatric surgery remains the most effective treatment option for the severely obese, yet many people do not choose to pursue it, as approximately only 1% of qualified patients undergo surgery.^{12,13} Given this low utilization rate among the severely obese, modest weight loss results with lifestyle treatment alone and the prevalence of obesity, there is a need for intermediate treatment options.

Results from this trial are consistent with the safety and efficacy profiles observed with the intragastric balloon in mostly

non-randomized trials outside the United States over the past 17 years. Based on a review of 17 published studies involving 1638 patients, the balloon resulted in median percent of excess over ideal weight loss of 27% (range 10.9–50.9)^{14–30} at 12 months (6 months after balloon removal), similar to the results from this trial. Furthermore, three previous small randomized controlled trials reported the percent of excess over ideal weight loss of 32, 33, and 17% over a control group at the time of balloon removal,^{30–32} similar to the 20% over the control group observed in this trial (6 months results not shown). Studies investigating the effects of the balloon on health conditions are few and short term, with only one randomized trial showing improvements in the metabolic syndrome.³⁰ The most common AEs reported with the balloon outside the United States were pain (34%), nausea (29%) and reflux (18%), whereas erosion or ulcer occurred in 14%, migration or bowel obstruction in 2% and death in 0.08%. The balloon was removed early, before the 6-month implantation time, in 7.5% of patients secondary to intolerance.³³ The early removal rate in this study (18.8%) was higher than that observed outside the United States and was largely due to device intolerance from GI symptoms and participant request. During the conduct of the trial, the medications used for treating the anticipated GI symptoms both varied between sites and evolved over time, which may have contributed to the early removal rate. There were no erosions, ulcers, deflations or migrations in this study.

A joint task force convened by the American Society for Gastrointestinal Endoscopy and the American Society for Metabolic and Bariatric Surgery defined acceptable thresholds of safety and efficacy for endoscopic bariatric therapies.^{34,35} The efficacy threshold for such a therapy intended as a primary obesity

Table 2b. Control group AEs with frequency $\geq 1\%$ control group ($N = 130$)

Event	Total, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
At least one AE	92 (70.8%)	67 (51.5%)	19 (14.6%)	6 (4.6%)
Sinusitis	19 (14.6%)	16 (12.3%)	3 (2.3%)	0 (0.0%)
Upper respiratory tract infection	13 (10.0%)	8 (6.2%)	5 (3.8%)	0 (0.0%)
Bronchitis	11 (8.5%)	6 (4.6%)	5 (3.8%)	0 (0.0%)
Back pain	10 (7.7%)	5 (3.8%)	4 (3.1%)	1 (0.8%)
Diarrhea	9 (6.9%)	6 (4.6%)	2 (1.5%)	1 (0.8%)
Arthralgia	9 (6.9%)	6 (4.6%)	3 (2.3%)	0 (0.0%)
Nausea	7 (5.4%)	5 (3.8%)	1 (0.8%)	1 (0.8%)
Vomiting	7 (5.4%)	5 (3.8%)	1 (0.8%)	1 (0.8%)
Nasopharyngitis	7 (5.4%)	6 (4.6%)	1 (0.8%)	0 (0.0%)
Headache	7 (5.4%)	5 (3.8%)	2 (1.5%)	0 (0.0%)
Constipation	6 (4.6%)	6 (4.6%)	0 (0.0%)	0 (0.0%)
Gastroesophageal reflux disease	6 (4.6%)	5 (3.8%)	1 (0.8%)	0 (0.0%)
Pharyngitis streptococcal	6 (4.6%)	5 (3.8%)	1 (0.8%)	0 (0.0%)
Hypertension	6 (4.6%)	4 (3.1%)	2 (1.5%)	0 (0.0%)
Abdominal pain	5 (3.8%)	2 (1.5%)	1 (0.8%)	2 (1.5%)
Impaired gastric emptying	5 (3.8%)	5 (3.8%)	0 (0.0%)	0 (0.0%)
Vitamin B1 decreased	5 (3.8%)	4 (3.1%)	1 (0.8%)	0 (0.0%)
Abdominal distension	4 (3.1%)	4 (3.1%)	0 (0.0%)	0 (0.0%)
Ear infection	4 (3.1%)	4 (3.1%)	0 (0.0%)	0 (0.0%)
Influenza	4 (3.1%)	4 (3.1%)	0 (0.0%)	0 (0.0%)
Blood thyroid-stimulating hormone decreased	4 (3.1%)	4 (3.1%)	0 (0.0%)	0 (0.0%)
Pain in extremity	4 (3.1%)	3 (2.3%)	1 (0.8%)	0 (0.0%)
Migraine	4 (3.1%)	2 (1.5%)	2 (1.5%)	0 (0.0%)
Vertigo	3 (2.3%)	2 (1.5%)	1 (0.8%)	0 (0.0%)
Dyspepsia	3 (2.3%)	2 (1.5%)	1 (0.8%)	0 (0.0%)
Fatigue	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Edema peripheral	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Seasonal allergy	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Viral infection	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Blood cholesterol increased	3 (2.3%)	2 (1.5%)	1 (0.8%)	0 (0.0%)
Blood potassium decreased	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Fluid retention	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Anxiety	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Menorrhagia	3 (2.3%)	2 (1.5%)	1 (0.8%)	0 (0.0%)
Cough	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Nasal congestion	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Sinus congestion	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Sleep apnea syndrome	3 (2.3%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Hiatus hernia	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
Respiratory tract infection	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
Skeletal injury	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
Bursitis	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
Sinus headache	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
Stress	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
Pharyngolaryngeal pain	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)

Abbreviations: AE, adverse events; IGB, intragastric balloon.

intervention was set at 25% excess of IBW measured at 12 months, with a statistically significant mean % excess of IBW difference between a primary endoscopic bariatric therapy and a control group of at least 15%. The threshold for incidence of serious AEs was set at 5% or less. The results of this trial confirm that the balloon system meets the prescribed efficacy threshold. There were 16 balloon subjects (10%–twice the 5% or less threshold) in this trial with serious AEs, half (8) of which were due to device intolerance leading to device removal. There were also some important limitations of this trial, including that it was short term and open label where both researchers and participants knew what treatment was being administered. In addition, the initial sponsor stopped enrollment before targets were met, which may have limited power for the coprimary end points, and *a priori* definitions of clinical significance for some measures of secondary end points (quality of life, depression) were not predetermined.

In conclusion, results from this trial show that adjunctive treatment with the IGB induces modestly greater short-term weight loss compared with lifestyle treatment alone and GI side effects are quite common. It is also not known if the differences in weight observed at 12 months after treatment (6 months after balloon removal) will be sustained with even longer follow-up. Further work needs to address patient satisfaction and more patient-centered outcomes and also identify individual factors that might predict better than average response to treatment.

CONFLICT OF INTEREST

AC has received research grants from the NIH-NIDDK, Nutrisystem, Ethicon J & J Healthcare, Covidien, is a consultant for Apollo Endosurgery for this project and was a project consultant for Ethicon J & J Healthcare. BAD is a consultant for Apollo Endosurgery and Xlumin. He has research agreements with Aspire Bariatrics and GI Dynamics. LE was a consultant to Allergan Medical while the study was being

conducted. She currently serves as a consultant to Apollo Endosurgery and is the principal consultant for Ultamed Corporation. JR was an employee of Allergan Medical during the close of the study but did not work on the trial, and currently serves as a consultant to Apollo Endosurgery. He currently is an employee of Simulstat. GW is a clinical trial investigator with USGI, ReShape and Obalon. MF is a former Allergan consultant and proctor. VS is a consultant for Apollo Endosurgery. He has research agreements with Apollo Endosurgery and Obalon as well as a clinical trial investigator for Obalon. HB is a consultant for Transenterix and speaker for Ethicon and Apollo Endosurgery. DP has nothing to disclose. CG is a consultant for Apollo Endosurgery and Olympus Corporation. He has performed sponsored research for Olympus Corporation and GI Supply. AC and JR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGEMENTS

The IB-005 Study Investigators included Nicholas Berth, MD (New Jersey), Helmut Billy, MD (California), Anita Courcoulas, MD (Pennsylvania), Timothy Ehrlich, MD (Connecticut), Mark Fusco, MD (Florida), Daniel Pambianco, MD (Virginia), Michael Snyder, MD (Colorado), George Woodman, MD (Tennessee), Colin Powers, MD (New York), Hans Joseph Schmidt, MD (New Jersey), Vafa Shayani, MD (Illinois), Peter Billing, MD (Washington), Thomas Chua, MD (Wisconsin), Lee Grossbard, MD (Florida) and Adam Smith, DO (Texas). The study was designed, funded and conducted by Allergan Medical, which was acquired by Apollo Endosurgery—the sponsor. The specific role of the sponsor for each of the following was: design and conduct of the study—sponsor initiated and led; data collection—study sites collected data that was then transmitted to sponsor; data management and study monitoring—sponsor led; statistical analysis—sponsor led, statistical analysis was provided by SimulStat Inc. and North American Science Associates (NAMSA), investigator and writing group input to analyses; interpretation of the data—study investigators and writing group members; preparation of manuscript—writing group; review of manuscript—writing group; approval of the manuscript—writing group; decision to submit the manuscript for publication—writing group.

REFERENCES

- Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 2014; **311**: 806–814.
- Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ *et al*. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010; **363**: 2211–2219.
- Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA *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**(Part B): 2985–3023.
- Mechanick JL, Garber AJ, Handelsman Y, Garvey WT. American Association of Clinical Endocrinologists' position statement on obesity and obesity medicine. *Endocr Pract* 2012; **18**: 642–648.
- The Practical Guide: *Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. National Institutes of Health: Bethesda, MD, USA; 2000. NIH publication 00-4084.
- Ryan DH, Johnson WD, Myers VH, Prather TL, McGlone MM, Rood J *et al*. Nonsurgical weight loss for extreme obesity in primary care settings: results of the Louisiana Obese Subjects Study. *Arch Intern Med* 2010; **170**: 146–154.
- Mechanick JL, Youdim A, Jones DB, Timothy Garvey W, Hurley DL, Molly McMahon M *et al*. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Surg Obes Rel Dis* 2013; **9**: 159–191.
- Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. *BMJ* 2014; **349**: g3961.
- Diabetes Prevention Program Research G, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ *et al*. 10-Year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; **374**: 1677–1686.
- Look ARG. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity* 2014; **22**: 5–13.

- Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA* 2014; **311**: 74–86.
- Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. *Obes Surg* 2013; **23**: 427–436.
- Fact Sheet. *Metabolic and Bariatric Surgery*. American Society for Metabolic and Bariatric Surgery. Available at: http://www.asbs.org/Newsite07/media/asmbfs_fs_surgery.pdf (last accessed 8 August).
- Sallet JA, Marchesini JB, Paiva DS, Komoto K, Pizani CE, Ribeiro MLB *et al*. Brazilian multicenter study of the intragastric balloon. *Obes Surg* 2004; **14**: 991–998.
- Herve J, Wahlen CH, Schaeken A, Dallemagne B, Dewandre JM, Markiewicz S *et al*. What becomes of patients one year after the intragastric balloon has been removed? *Obes Surg* 2005; **15**: 864–870.
- Angrisani L, Lorenzo M, Borrelli V, Giuffrè M, Fonderico C, Capece G. Is bariatric surgery necessary after intragastric balloon treatment? *Obes Surg* 2006; **16**: 1135–1137.
- Ganesh R, Rao AD, Baladas HG, Leese T. The Bioenteric Intragastric Balloon (BIB) as a treatment for obesity: poor results in Asian patients. *Singap Med J* 2007; **48**: 227–231.
- Genco A, Balducci S, Bacci V, Materia A, Cipriano M, Baglio G *et al*. Intragastric balloon or diet alone? A retrospective evaluation. *Obes Surg* 2008; **18**: 989–992.
- Crea N, Pata G, Della Casa D, Minelli L, Maifredi G, Di Betta E *et al*. Improvement of metabolic syndrome following intragastric balloon: 1 year follow-up analysis. *Obes Surg* 2009; **19**: 1084–1088.
- Genco A, Cipriano M, Materia A, Bacci V, Maselli R, Musmeci L *et al*. Laparoscopic sleeve gastrectomy versus intragastric balloon: a case-control study. *Surg Endosc* 2009; **23**: 1849–1853.
- Ohta M, Kitano S, Kai S, Shiromizu A, Eguchi H, Endo Y *et al*. Initial Japanese experience with intragastric balloon placement. *Obes Surg* 2009; **19**: 791–795.
- Al Kahtani K, Khan MQ, Helmy A, Al Ashgar H, Rezeig M, Al Quaziz M *et al*. Bioenteric intragastric balloon in obese patients: a retrospective analysis of King Faisal Specialist Hospital experience. *Obes Surg* 2010; **20**: 1219–1226.
- Mui WL-M, Ng EK-W, Tsung BY-S, Lam CH, Yung MY. Impact on obesity-related illnesses and quality of life following intragastric balloon. *Obes Surg* 2010; **20**: 1128–1132.
- Genco A, Cipriano M, Bacci V, Maselli R, Paone E, Lorenzo M *et al*. Intragastric balloon followed by diet vs intragastric balloon followed by another balloon: a prospective study on 100 patients. *Obes Surg* 2010; **20**: 1496–1500.
- Kotzampassi K, Grosomanidis V, Papakostas P, Penna S, Eleftheriadis E. 500 intragastric balloons: what happens 5 years thereafter? *Obes Surg* 2012; **22**: 896–903.
- Nikolic M, Boban M, Ljubicic N, Supanc V, Mirosevic G, Pezo Nikolic B *et al*. Morbidly obese are ghrelin and leptin hyporesponders with lesser intragastric balloon treatment efficiency: ghrelin and leptin changes in relation to obesity treatment. *Obes Surg* 2011; **21**: 1597–1604.
- Bozkurt S, Coskun H. The early results of intragastric balloon application of different BMI groups. *Eur Surg Acta Chirurg Austri* 2012; **44**: 383–387.
- Farina MG, Baratta R, Nigro A, Vinciguerra F, Puglisi C, Schembri R *et al*. Intragastric balloon in association with lifestyle and/or pharmacotherapy in the long-term management of obesity. *Obes Surg* 2012; **22**: 565–571.
- Dogan UB, Gumurdulu Y, Akin MS, Yalaki S. Five percent weight lost in the first month of intragastric balloon treatment may be a predictor for long-term weight maintenance. *Obes Surg* 2013; **23**: 892–896.
- Fuller NR, Pearson S, Lau NS, Włodarczyk J, Halstead MB, Tee HP *et al*. An intragastric balloon in the treatment of obese individuals with metabolic syndrome: a randomized controlled study. *Obesity* 2013; **21**: 1561–1570.
- Genco A, Cipriano M, Bacci V, Cuzzolaro M, Materia A, Raparelli L *et al*. BioEnterics Intragastric Balloon (BIB): a short-term, double-blind, randomised, controlled, crossover study on weight reduction in morbidly obese patients. *Int J Obes* 2006; **30**: 129–133.
- Mohammed MA, Anwar R, Mansour AH, Elmasry E, Othman G. Effects of intragastric balloon versus conservative therapy on appetite regulatory hormones in obese subjects. *Trends Med Res* 2014; **9**: 58–80.
- Force ABET, Committee AT, Abu Dayyeh BK, Edmundowicz SA, Jonnalagadda S, Kumar N *et al*. Endoscopic bariatric therapies. *Gastrointest Endosc* 2015; **81**: 1073–1086.
- Therapy AATFoEB. A pathway to endoscopic bariatric therapies. *Surg Obes Rel Dis* 2011; **7**: 672–682.
- Therapy AATFoEB, Ginsberg GG, Chand B, Cote GA, Dallal RM, Edmundowicz SA *et al*. A pathway to endoscopic bariatric therapies. *Gastrointest Endosc* 2011; **74**: 943–953.

Supplementary Information accompanies this paper on International Journal of Obesity website (<http://www.nature.com/ijo>)