

ORIGINAL ARTICLE

Clinical Trials and Investigations

Efficacy and safety of a novel oral hydrogel capsule in adults with overweight or obesity: the pivotal randomized RESET study

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Abstract

Objective: The objective of this study was to investigate the efficacy and safety of the Epitomee capsule versus placebo as an adjunct to high-intensity lifestyle intervention in participants with overweight or obesity.

Methods: The Randomized Evaluation of Efficacy and Safety of the Epitomee Capsule Trial (RESET) was a prospective, double-blind, placebo-controlled pivotal trial in adults with baseline BMI of 27.0 to 40.0 kg/m². The co-primary endpoints at week 24 were percentage change from baseline in body weight for the Epitomee and placebo groups and proportion of Epitomee-treated patients achieving ≥5% weight loss compared with a 35% threshold. The primary safety endpoint was the incidence of device-related serious adverse events.

Results: A total of 138 participants received Epitomee and 141 received placebo. Mean (SD) change in body weight from baseline was −6.6% (6.5%) with Epitomee and −4.6% (4.7%) with placebo; least-squares means were −6.1% (0.6%) and −4.2% (0.6%), respectively ($p = 0.0054$). Fifty-six percent of Epitomee-treated participants attained ≥5% weight loss from baseline, which was significantly greater than the 35% predefined threshold ($p < 0.0001$). Twenty-seven percent of Epitomee-treated and eleven percent of placebo-treated participants achieved ≥10% weight loss. Adverse event rates were similar between the groups. No device-related serious adverse events occurred.

Conclusions: The Epitomee capsule is a safe and efficacious nonpharmacological option for weight management with potential broad application in participants with overweight or obesity.

Clinical trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04222322): NCT04222322.

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INTRODUCTION

Approximately 2.5 billion adults worldwide have overweight, including 890 million adults with obesity [1]. Obesity was recognized by the World Health Organization as a global epidemic as early as 1997, and the prevalence of obesity has doubled in more than 70 countries since 1990 and has continuously increased in most others [2, 3]. Overweight and obesity are associated with increased risks of morbidity, including type 2 diabetes and cardiovascular disease [4].

Obesity is a heterogeneous, chronic, and progressive disease [5]. Several pathways regulate energy balance and provide a feedback loop among energy intake, energy expenditure, and body energy stores [6]. Comprehensive lifestyle intervention, consisting of a calorie-restricted diet, increased physical activity, and behavioral therapy to facilitate treatment engagement, is recommended for weight loss in individuals with overweight or obesity [7]. To increase weight loss, lifestyle intervention can be combined with adjunctive therapies, including pharmacotherapies or surgeries that target different aspects of energy regulation [7]. For example, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) mimic hormones that have peripheral and central actions to reduce appetite [8–10], and lipase inhibitors prevent the breakdown and absorption of fats in the intestines [11]. However, both types of therapy are commonly associated with gastrointestinal side effects [8, 9, 11, 12]. Surgical interventions are associated with significant weight loss but are invasive and can result in complications and serious side effects [13]. Considering the heterogeneous, chronic, and progressive nature of obesity [5], a one-size-fits-all approach is not appropriate. Thus, having a variety of available treatment approaches allows treatment to be tailored to patients' needs and preferences. For individuals with overweight or obesity who are at lower risk of morbidity, there is an unmet need for early, minimally invasive interventions that can help patients reduce their energy intake and attain moderate weight loss, with a lower risk of side effects than that associated with most current pharmacotherapies and surgeries for obesity.

The Epitomee capsule is a novel, minimally invasive, drug-free, oral, self-administered medical device for weight management in individuals with overweight or obesity. It is composed of absorbent polymers and bonding materials that self-expand in the stomach to create a gel-based, space-occupying structure (Figure 1). This structure resists the peristaltic waves of the stomach and is hypothesized to activate sensory mechanoreceptors and the gut-brain axis signaling pathway to promote early signaling of satiety before dissolving and being excreted via the gastrointestinal tract. This mechanism of action is mechanical and does not involve any direct chemical activity.

In a prospective, 12-week, single-arm study that enrolled 78 participants with overweight or obesity, twice-daily administration of the Epitomee capsule in combination with lifestyle counseling was associated with a mean (SD) reduction in body weight from baseline of 3.7% (3.1%) in the intention-to-treat analysis and 4.5% (3.0%) in the per-protocol analysis ($p < 0.001$) [14]. Weight loss was correlated with self-reported early satiety, decreased snacking, and reduced meal size and was accompanied by improvements in cardiometabolic risk factors, including waist circumference, systolic and diastolic blood

Study Importance

What is already known?

- The Epitomee capsule is a novel, oral, self-administered medical device for weight management, consisting of superabsorbent, pharmaceutical-grade polymers and bonding materials that self-expand in the stomach to form a triangular gel scaffold.
- In a prospective, single-arm, 12-week study in participants with overweight or obesity, the Epitomee capsule significantly reduced body weight, improved cardiometabolic risk factors and satiety, and had a favorable safety profile.

What does this study add?

- In this prospective, 24-week, randomized, double-blind, placebo-controlled pivotal study, the addition of the Epitomee capsule to lifestyle intervention demonstrated efficacy for weight loss; both co-primary efficacy endpoints were met.
- Adverse event rates were similar for the Epitomee and placebo groups, and no device-related serious adverse events were observed, which supports a favorable safety profile of the Epitomee capsule.

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

- The Epitomee capsule is a safe and effective option for weight management in patients with overweight or obesity and appears appropriate as an early intervention to induce moderate weight loss, including in individuals with obesity-related complications such as prediabetes.

pressure, and triglyceride levels [14, 15]. The Epitomee capsule had a favorable safety and tolerability profile, with no device-related serious adverse events (SAEs) [14].

Herein, we report the results of the Randomized Evaluation of Efficacy and Safety of the Epitomee Capsule Trial (RESET) [16], which assessed the efficacy and safety of the Epitomee capsule compared with placebo, each as an adjunct to lifestyle counseling, in reducing body weight at 24 weeks, in participants with overweight or obesity.

METHODS

Trial design

RESET was a prospective, randomized, double-blind, placebo-controlled, multicenter pivotal trial conducted in the United States.



FIGURE 1 The Epitomee capsule before and after oral administration. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/oby.24240)]

Participants were enrolled between September 2020 and January 2023. The study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guidelines for Good Clinical Practice, International Organization for Standardization (ISO) 14155:2011, the US Codes of Federal Regulations (21 CFR parts 11, 50, 54, 56, 812, and 814), and the Declaration of Helsinki. Written approval was obtained from the appropriate institutional review boards at each site before site activation (Table S1). A signed informed consent form was obtained from each participant before performing any study-related activities or evaluations.

Objective

The primary objective of the study was to compare the percentage change from baseline in body weight at 24 weeks with the Epitomee capsule versus a visually matching placebo capsule, each in combination with a high-intensity lifestyle intervention program, in participants with overweight or obesity and with or without prediabetes.

The Epitomee capsule is composed of pharmaceutical-grade polymers and bonding materials and consists of an outer capsule and a flexible envelope film that encloses a layer of hydrogel particles (Figure 1). In the stomach, the outer capsule dissolves and the perforated envelope film allows water and stomach fluid to enter the envelope film. Water is then absorbed by the dry hydrogel particles enclosed within the envelope film, which self-expands to form a semirigid, triangular gel scaffold. The capsule was designed to require as little hydrogel as possible while having relatively large dimensions when expanded. After several hours in the stomach, the triangular structure collapses, allowing it to pass into the intestine, where the envelope film disintegrates and the hydrogel particles are then excreted naturally via the gastrointestinal tract.

Participants

To be eligible for the study, participants were required to be at least 18 years old at screening and have a body mass index (BMI) of 27.0 to 40.0 kg/m² inclusive. Participants had a glycated hemoglobin level of no more than 6.4% and fasting glucose of less than 126 mg/dL. Participants who had prediabetes could be untreated or receiving a stable dose of metformin (≤ 2000 mg per day) for at least 4 months. Participants were required to have previously attempted to lose weight unsuccessfully using a medically supervised or self-directed diet but to have had no prior use of any gastric medical device or any intent to undergo gastric surgery or banding during the study period. Participation in any clinical study within the past 3 months was not allowed. In addition, participants were required to demonstrate their ability and willingness to complete the physical activity program and to maintain the calorie-controlled diet in accordance with the study program. Full details of the inclusion and exclusion criteria are included in Table S2.

Procedures

The study consisted of a screening period of up to 4 weeks, including a screening visit, 3-day run-in period, and washout period of at least 3 days before randomization. During the 3-day run-in period, participants were required to take open-label placebo capsules, track physical activity, and weigh using a portable weight scale; they were also asked to track capsule and daily food intake using the study mobile app. Participants were subsequently interviewed via a call to assess compliance and adverse events (AEs) during the run-in period. The study mobile app data were reviewed by study personnel to confirm eligibility. During the washout period, participants did not receive treatment or use the physical activity tracker, portable weight scale, or study mobile app.

Following screening, eligible participants were randomized in a 1:1 ratio using an interactive web response system to receive, for

24 weeks, either the Epitomee capsule plus a high-intensity lifestyle intervention or placebo with the same lifestyle intervention. Study investigators, participants, and the sponsor were masked to treatment group. Participants were considered to be enrolled after randomization and were instructed to take one Epitomee or placebo capsule with at least two full cups of water (16 oz or 480 mL) twice daily 30 min before eating a main meal (preferably lunch and dinner).

The lifestyle intervention program included instructions for diet and physical activity modification, delivered over 24 weeks in 14 lifestyle counseling sessions of approximately 15 min each. Lifestyle counseling sessions were weekly in the first month and every other week thereafter and were provided by a registered dietitian, nurse practitioner, clinical or health psychologist, or research nurse. Lifestyle counseling was conducted remotely in cases of restrictions due to the COVID-19 pandemic or when participants were otherwise unable to attend a scheduled clinic visit. Participants were instructed to consume a diet of 1200 to 1800 calories per day based on their baseline body weight and to gradually increase their physical activity to 180 min or more per week by week 24. The program was developed in accordance with clinical guidelines for the Management of Overweight and Obesity in Adults [7, 17] and was shown in two prior randomized trials to reduce body weight by ~4% to 5% at 24 to 28 weeks [18, 19]. Additional details on the lifestyle intervention program are provided in Table S3.

A safety follow-up assessment was conducted 4 weeks after treatment completion (week 28). The full schedule of study assessments and procedures is included in Table S4.

Endpoints

The protocol prespecified co-primary efficacy endpoints. The first co-primary endpoint was the mean percentage change from baseline in body weight at week 24 in the Epitomee and placebo groups. The second co-primary endpoint was the proportion of responders, defined as participants with at least 5% weight loss from baseline, at week 24 in the Epitomee group, which was compared with the predefined threshold of 35% of participants. Secondary efficacy endpoints included the proportion of participants with at least 7.5% or at least 10% weight loss from baseline at week 24 and reduction in BMI from baseline to week 24.

The primary safety endpoint was the incidence of device-related SAEs from randomization through week 24. Secondary safety endpoints included incidents of all AEs coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Statistical analysis

An adaptive study design was specified to enable sample size reestimation. Trials with an adaptive design are often more efficient than trials with a traditional fixed design because they often make better use of resources (e.g., time and money) and may require fewer

participants [20]. Adaptation of sample size was conducted using the Mehta and Pocock method [21] with a lower bound of 115 participants per group (total, $N = 230$) and an upper bound of 300 participants per group (total, $N = 600$). Sample size reestimation was conducted in a masked manner after 70 participants in each group completed 24 weeks of treatment.

The full analysis set included all randomized participants who consumed at least one study capsule (Epitomee or placebo) after randomization, had their weight recorded at baseline, and had at least one post-baseline assessment. All efficacy analyses were conducted in the full analysis set. The safety set was defined as participants who consumed at least one study capsule (Epitomee or placebo) after randomization.

Baseline characteristics were analyzed in the full analysis set using descriptive statistics. Continuous variables were analyzed using Student *t* test and summarized using mean (SD), minimum, median, and maximum values. Categorical variables were analyzed by Fisher exact test and summarized using numbers of observations and percentages. Adherence to capsule use was objectively calculated by trained site personnel, who determined adherence by dividing the number of capsules taken (based on the number of capsules returned) by the expected number of capsules (the required intake).

For the first co-primary efficacy endpoint, the analysis compared percentage change from baseline in body weight, at week 24, for the Epitomee and placebo groups using ANCOVA with missing data imputed using robust multiple imputation analysis. The analysis compared the estimated least-squares mean difference at week 24 between the treatment groups. The null hypothesis of no difference between the treatment groups was rejected if the confidence interval (CI) for the difference between Epitomee and placebo excluded zero. The second co-primary endpoint for whether the proportion of responders in the Epitomee group exceeded the 35% threshold was assessed using a binominal test for proportions.

Post hoc analyses were conducted using logistic regression to compare the proportion of participants treated by Epitomee versus placebo who achieved different percentages of weight loss from baseline to week 24.

Safety endpoints were analyzed in the safety dataset using the prespecified MedDRA system set and included the number of incidents of AEs and the number and percentage of participants who experienced AEs.

Statistical analyses were performed using SAS version 9.4 or higher (Windows 2008 Terminal; SAS Institute Inc.).

RESULTS

Study participants

Of the 444 individuals screened for eligibility, 279 were randomized, with 138 allocated to the Epitomee group and 141 to the placebo group (Figure 2). All randomized participants received the allocated intervention.

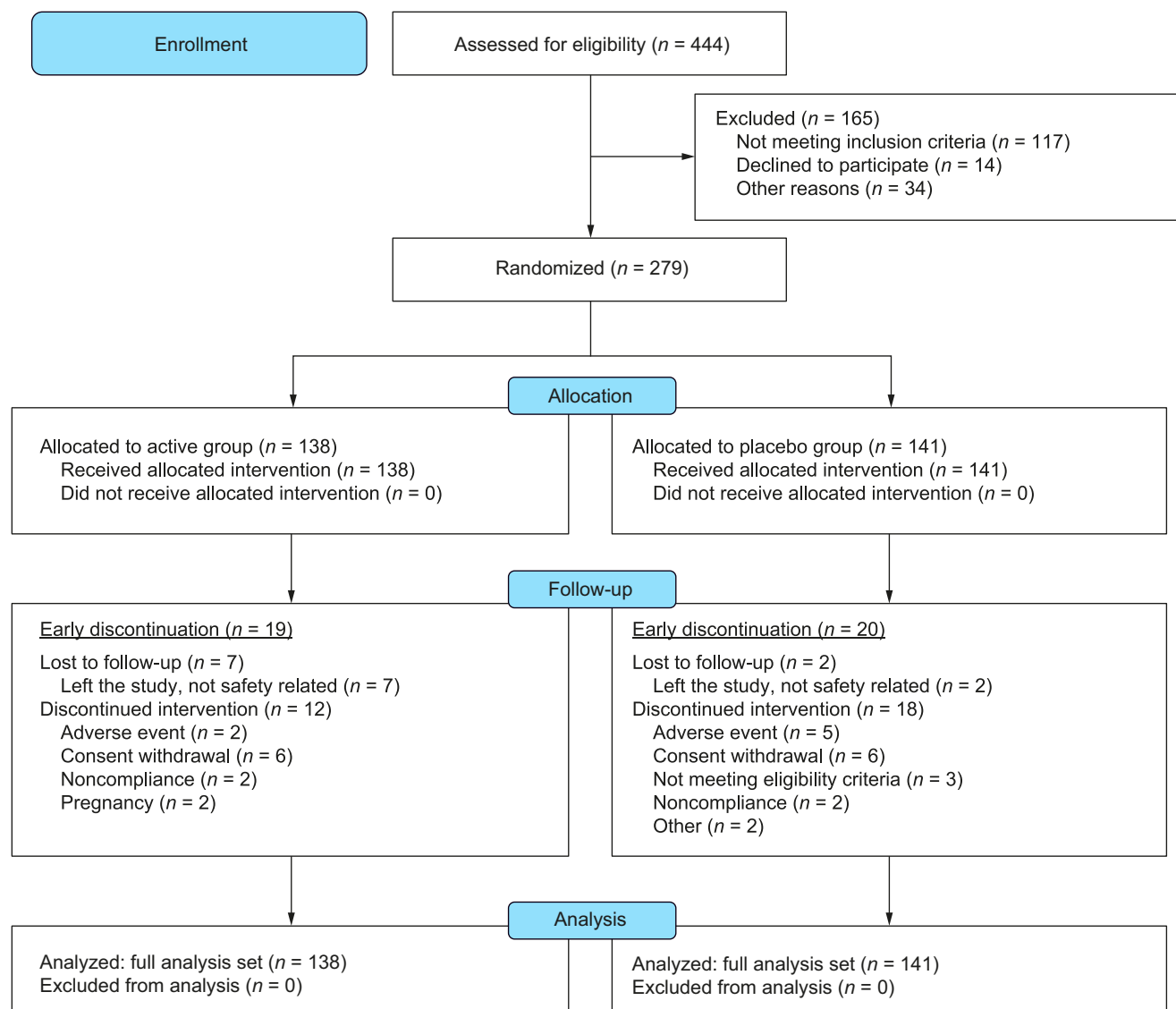


FIGURE 2 Participant disposition. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/oby.24240)]

Overall, the majority of participants in the Epitomee and placebo groups were female (80.4% and 79.4%, respectively) and White (70.3% and 65.2%, respectively). There were no significant differences between the Epitomee and placebo groups regarding sex, race and ethnicity, and age (Table 1).

In the Epitomee group, mean baseline body weight was 95.9 (SD 15.4) kg, mean BMI was 34.1 (SD 3.3) kg/m², and mean waist circumference was 104.3 (SD 9.9) cm for women and 116.8 (SD 10.3) cm for men. Values were similar for participants in the placebo group (Table 1). Glycemic status was similar between groups: 57.2% and 63.8% of participants had normoglycemia and 39.1% and 35.5% of participants had prediabetes in the Epitomee and placebo groups, respectively.

Capsule adherence was high in both groups: participants assigned to Epitomee took 96.2% of the expected doses, and those assigned to placebo took 98.3% of doses over the 24 weeks.

Efficacy

For the first co-primary efficacy endpoint, mean (SD) percentage change from baseline in body weight at week 24 was -6.6% (6.5%) for the Epitomee group and -4.6% (4.7%) for placebo. The least-squares mean was significantly greater for the Epitomee group, i.e., mean (standard error [SE]) of -6.1% (0.6%) versus -4.2% (0.6%; $p = 0.0054$). Significantly greater weight loss with Epitomee versus placebo was observed as early as week 4 ($p < 0.05$), and weight loss continued for the entire treatment period (Figure 3).

For the second co-primary efficacy endpoint, 56% of participants in the Epitomee group attained at least 5% weight loss from baseline at week 24, which was significantly greater than the 35% predefined threshold ($p < 0.0001$; Figure 4). In a post hoc analysis, the proportion of participants who attained at least 5% weight loss from baseline in Epitomee treatment was 56% versus 44% in the placebo group

TABLE 1 Baseline demographics and clinical characteristics.

	Epitomee <i>n</i> = 138	Placebo <i>n</i> = 141	Difference ^a (95% CI)	<i>p</i> value
Sex, % (<i>n</i> / <i>N</i>)				0.8818
Female	80.4 (111/138)	79.4 (112/141)	1.0 (−8.4 to 10.4)	
Male	19.6 (27/138)	20.6 (29/141)	−1.0 (−10.4 to 8.4)	
Race or ethnicity, % (<i>n</i> / <i>N</i>)				0.6050
White	70.3 (97/138)	65.2 (92/141)	5.0 ^a (−5.9 to 16.0)	
Black or African American	21.0 (29/138)	24.1 (34/141)	−3.1 (−12.9 to 6.7)	
Asian	1.4 (2/138)	3.5 (5/141)	−2.1 (−5.7 to 1.5)	
American Indian or Alaska Native	0.7 (1/138)	1.4 (2/141)	−0.7 (−3.1 to 1.7)	
Multiple	2.9 (4/138)	5.0 (7/141)	−2.1 (−6.6 to 2.5)	
Unknown/not reported	1.4 (2/138)	0.0 (0/141)	1.4 (−0.5, 3.4)	
Hispanic or Latino, % (<i>n</i> / <i>N</i>)	2.2 (3/138)	0.7 (1/141)	1.5 (−1.3 to 4.3)	
Age, y, mean (SD), <i>n</i>	48.5 (12.5), 138	48.6 (12.4), 141	−0.1 (−3.1 to 2.8)	0.9222
Weight, kg, mean (SD), <i>n</i>	95.9 (15.4), 138	95.7 (15.4), 141	0.1 (−3.5 to 3.8)	0.9409
BMI, kg/m ² , mean (SD), <i>n</i>	34.1 (3.3), 138	33.7 (3.4), 141	0.4 (−0.4 to 1.2)	0.3197
Weight categories, % (<i>n</i> / <i>N</i>)				0.1454
Overweight (BMI, 25.0–29.9 kg/m ²)	9.4 (13/138)	16.3 (23/141)	−6.9 (−14.7 to 0.9)	
Class I obesity (BMI, 30.0–34.9 kg/m ²)	47.8 (66/138)	44.7 (63/141)	3.1 (−8.6 to 14.8)	
Class II obesity (BMI, 35.0–39.9 kg/m ²)	39.1 (54/138)	38.3 (54/141)	0.8 (−10.6 to 12.3)	
Class III obesity (BMI ≥40.0 kg/m ²)	3.6 (5/138)	0.7 (1/141)	2.9 (−0.5 to 6.3)	
Waist circumference, cm, mean (SD), <i>n</i>	106.7 (11.1), 138	107.6 (11.7), 141	−0.9 (−3.6 to 1.8)	0.5124
Female	104.3 (9.9)	104.2 (9.5)	−4.0 (−9.3 to 1.3)	0.9628
Male	116.8 (10.3)	120.8 (10.0)	−4.0 (−9.3 to 1.3)	0.1489
Glycemic status, % (<i>n</i> / <i>N</i>)				0.3790
Missing	1.4 (2/138)	0.0 (0/141)	1.4 (−1.4 to 5.1)	
Normoglycemia ^b	57.2 (79/138)	63.8 (90/141)	−6.6 (−17.8 to 4.8)	
Prediabetes ^c	39.1 (54/138)	35.5 (50/141)	3.6 (−7.6 to 14.8)	
Diabetes ^d	2.2 (3/138)	0.7 (1/141)	1.5 (−2.0 to 5.5)	
LDL cholesterol, mg/dL, mean (SD), <i>n</i>	116.5 (31.4), 136	117.0 (31.2), 139	−0.5 (−8.0 to 6.9)	0.8885
HDL cholesterol, mg/dL, mean (SD), <i>n</i>	56.3 (14.9), 136	54.6 (15.3), 139	1.8 (−1.8 to 5.3)	0.3352
Systolic blood pressure, mm Hg, mean (SD), <i>n</i>	120.9 (14.2), 138	121.1 (13.4), 141	−0.1 (−3.4 to 3.1)	0.9311
Diastolic blood pressure, mm Hg, mean (SD), <i>n</i>	77.3 (10.6), 138	77.9 (9.2), 141	−0.6 (−2.9 to 1.7)	0.6124
Fasting glucose, mg/dL, mean (SD), <i>n</i>	91.3 (10.9), 135	91.6 (10.1), 137	−0.2 (−2.7 to 2.3)	0.8530
HbA1c, %, mean (SD), <i>n</i>	5.5 (0.3), 136	5.5 (0.3), 141	0.0 (−0.1 to 0.1)	0.8540
Triglycerides, mean (SD), <i>n</i>	111.5 (55.8), 136	110.1 (50.5), 139	1.4 (−11.2 to 14.0)	0.8295
Current smoker, % (<i>n</i> / <i>N</i>)	2.2 (3/138)	2.1 (3/141)	0.0 (−3.4 to 3.5)	1.0000

Abbreviations: HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^aDifference between variables was calculated prior to rounding.

^bFasting plasma glucose < 100 mg/dL and/or HbA1c < 5.7%.

^cFasting plasma glucose between ≥100 mg/dL and <126 mg/dL and/or HbA1c between ≥ 5.7% and <6.4%.

^dFour ineligible participants with diabetes were included by mistake. Study's medical monitor and the responsible principal investigators decided to allow their continued participation.

($p = 0.0732$). In addition, the proportion of participants who attained at least 10% weight loss from baseline was significantly greater in the Epitomee group than in the placebo group (27% vs. 11%; $p < 0.002$; Figure 4). The proportion of participants who attained at least 15% weight loss from baseline was 11% in the Epitomee group and 6% in

the placebo group ($p = 0.1539$; Figure 4). Waterfall plots that illustrate individual body weight changes at week 24 are shown in Figure S3.

Participants who received Epitomee had a 2.3-fold increase in the odds of achieving weight loss from baseline of at least 7.5%

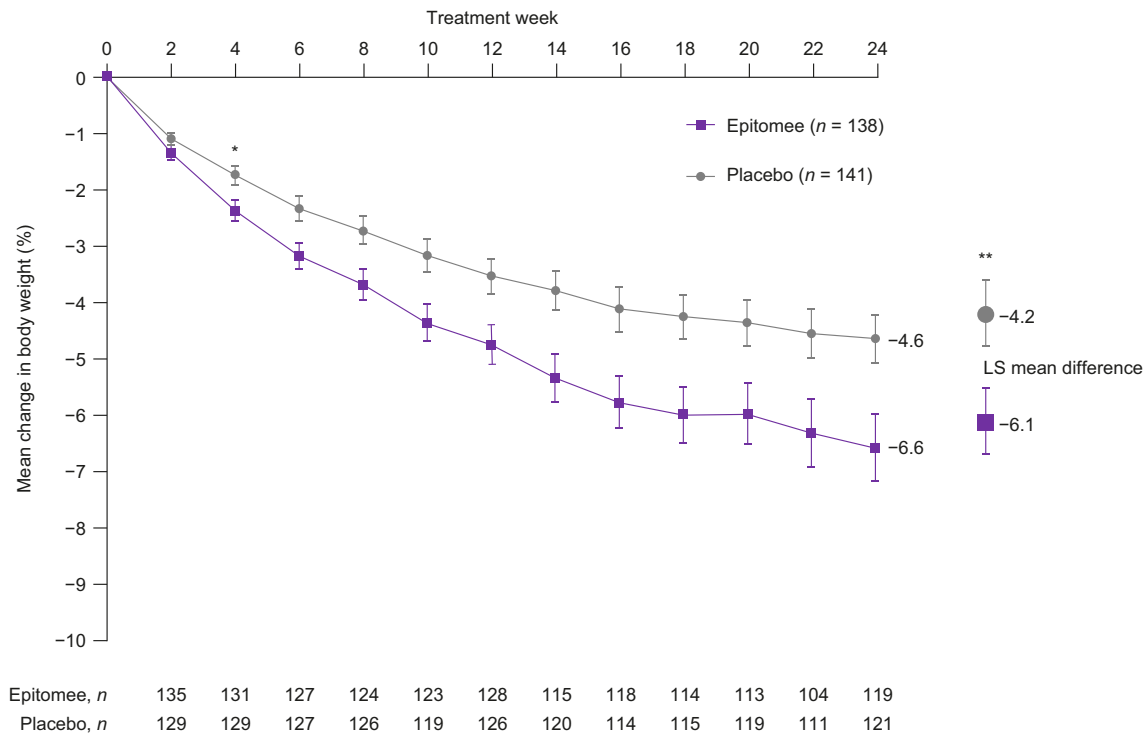


FIGURE 3 Mean percent change in body weight from baseline to week 24 in the full analysis set. * $p < 0.05$; ** $p = 0.0054$. LS, least-squares. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/oby.24240)]

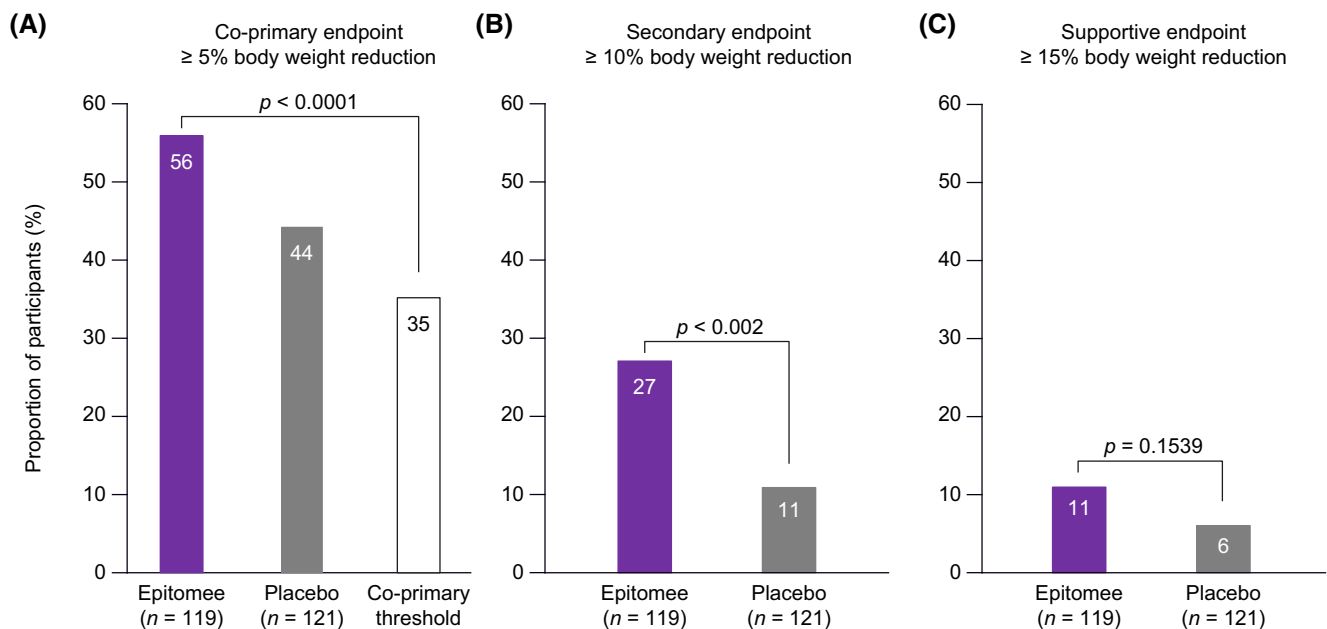


FIGURE 4 Proportion of participants in the full analysis set with a reduction in body weight from baseline to week 24 of at least 5%, at least 10%, and at least 15%. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/oby.24240)]

($p < 0.004$) compared with those who received placebo and a 3.1-fold increase in the odds of achieving a weight loss of at least 10% ($p = 0.0019$; Figure S1).

Participants who received Epitomee had a significantly greater mean reduction in BMI than those assigned to placebo ($p = 0.0001$;

Figure S2). Post hoc analysis of the cumulative frequency distributions for percentage change from baseline in body weight revealed that a significantly greater proportion of participants in the Epitomee group had weight reduction from baseline of 5.5% to 12.5% of body weight than those in the placebo group ($p < 0.05$; Figure S2).

Safety

AEs were experienced by 86.2% and 84.4% of participants in the Epitomee and placebo groups, respectively ($p = 0.7363$; Table 2). The number of AEs was also similar, with 357 and 368 events in the Epitomee and placebo groups, respectively. Most AEs were mild in severity. The proportion of participants who experienced device-related AEs was similar for the Epitomee (30.4%) and placebo groups (34.8%; $p = 1.000$). Two participants experienced SAEs: one participant in the Epitomee group experienced a *Helicobacter pylori*-related gastric ulcer, and one participant in the placebo group experienced a transient ischemic attack. There were no device-related SAEs.

The most common system organ classes affected by AEs were infections or infestations (Epitomee, 46% of participants; placebo, 45% of

participants; $p = 1.0000$), which was expected because the study took place during the COVID-19 pandemic, followed by gastrointestinal disorders (Epitomee, 39% of participants; placebo, 40% of participants; $p = 0.8071$; Figure 6). The AEs experienced by participants were also similar between the treatment groups (Figure 6). The most common AEs in the Epitomee group were upper respiratory tract infection (12%), nasopharyngitis (11%), COVID-19 (11%), constipation (9%), headache (7%), and abdominal pain (7%). In the placebo group, constipation (16%), COVID-19 (11%), nasopharyngitis (10%), nausea (10%), upper respiratory tract infection (8%), diarrhea (6%), and headache (6%) were most common.

Overall, 39 participants (14%) discontinued treatment during the study; participants who discontinued were evenly distributed across the Epitomee ($n = 19$) and placebo ($n = 20$) groups. More participants discontinued owing to AEs in the placebo group (3.5%) than in the Epitomee group (1.4%).

DISCUSSION

The Epitomee capsule met both co-primary efficacy endpoints in the present study. It induced a significantly greater mean percentage reduction from baseline in body weight than placebo at week 24 (6.6% vs. 4.6%, respectively), and 56% of Epitomee-treated participants had at least 5% weight loss from baseline, exceeding a predefined threshold of 35% of participants. In a post hoc analysis, a significantly greater proportion of participants who received Epitomee than participants who received placebo lost 5.5% to 12.5% of body weight. Furthermore, participants who received Epitomee had a significantly greater mean reduction from baseline in BMI at week 24 than those who received placebo. Collectively, these results suggest that the Epitomee capsule is

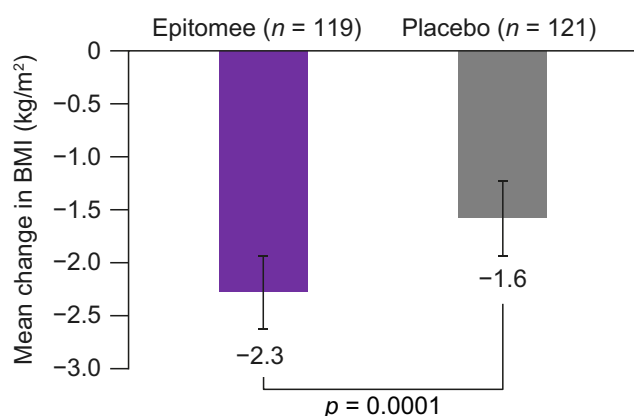


FIGURE 5 Mean (SE) change in BMI from baseline to week 24 in the full analysis set. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

TABLE 2 Frequency of AEs and SAEs.

	Epitomee (n = 138)		Placebo (n = 141)		p value
	Participants, n (%)	Events, n	Participants, n (%)	Events, n	
Any AE	119 (86.2)	357	119 (84.4)	368	0.7363
Severity					
Mild AE	107 (77.5)	244	109 (77.3)	258	1.0000
Moderate AE	51 (37.0)	97	49 (34.8)	92	0.7099
Severe AE	12 (8.7)	16	11 (7.8)	18	0.8303
Causality					
Related AE	42 (30.4)	62	49 (34.8)	83	1.0000
Unrelated AE	111 (80.4)	295	109 (77.3)	285	0.4472
SAE	1 (0.7)	1	1 (0.7)	1	0.5595
Device-related SAE as assessed by PI	0 (0.0)	0	0 (0.0)	0	
GI-related AE as assessed by PI	37 (26.8)	51	45 (31.9)	74	0.3609
Mild	28 (20.3)	39	33 (23.4)	60	0.5643
Moderate	9 (6.5)	12	11 (7.8)	13	0.8174
Severe	0 (0)	0	1 (0.7)	1	1.0000

Abbreviations: AE, adverse event; GI, gastrointestinal; PI, principal investigator; SAE, serious adverse event.

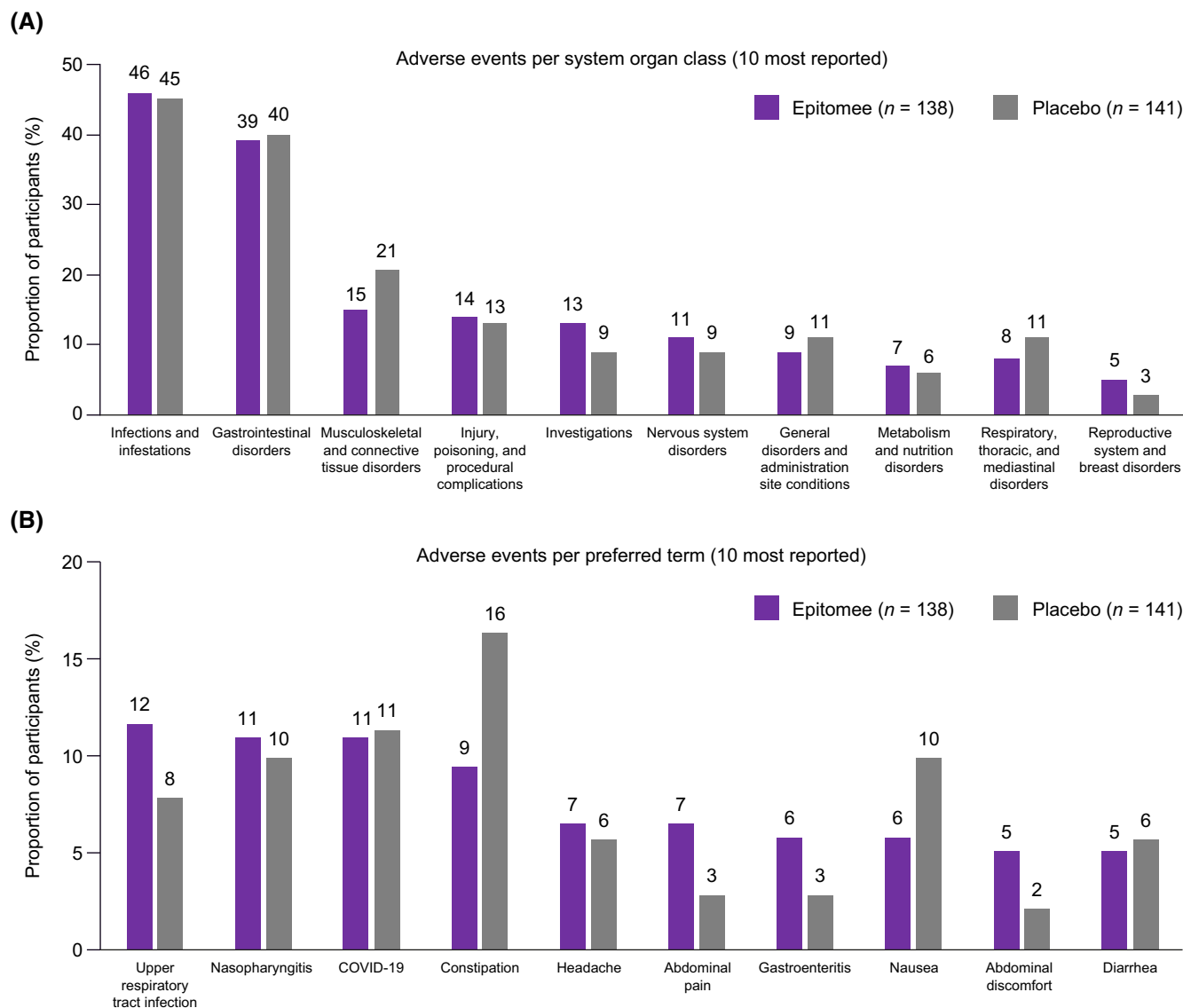


FIGURE 6 Proportion of participants with adverse events (A) per system organ class and (B) per preferred term (10 most reported) in the safety dataset using the prespecified MedDRA system. MedDRA, Medical Dictionary for Regulatory Activities. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/terms-and-conditions)]

an effective intervention for the attainment of moderate weight loss as an adjunct to high-intensity lifestyle intervention. Previous studies have demonstrated that a 5% to 7% reduction in body weight, consistent with the observed weight loss with Epitomee, is associated with clinically relevant improvements in cardiovascular disease risk factors, including a reduction in the risk of developing type 2 diabetes in patients with overweight or obesity who have prediabetes or are at high risk of type 2 diabetes [22–27].

Adherence to capsule intake was high for both the Epitomee and placebo groups, and the Epitomee capsule was well tolerated. The rate of AEs was similar for the Epitomee and placebo groups, and there were similarities in the organ classes affected and the types of AEs. The most common organ class affected by AEs in both groups was infections and infestations, which is likely because RESET was conducted during the COVID-19 pandemic, followed by

gastrointestinal disorders. Notably, there were no device-related SAEs. Participant retention was high, which may be partly attributable to the favorable tolerance and safety profile of Epitomee capsule.

The mean treatment effect in this study achieved with the Epitomee capsule combined with high-intensity lifestyle intervention was comparable with that attained at 28 weeks with liraglutide, combined with the same frequency of lifestyle intervention. Specifically, in the Satiety and Clinical Adiposity—Liraglutide Evidence in individuals with and without diabetes intensive behavioral therapy randomized controlled trial, mean body weight change with liraglutide was –8.4%, compared with –5.4% for placebo [18]. Although the Epitomee capsule clearly induces less weight loss than newer GLP-1 RAs (e.g., semaglutide), it also appears to be associated with fewer AEs than both liraglutide and the recently approved GLP-1 RAs [8, 9, 18, 28, 29], although head-to-head trials are needed to investigate this hypothesis.

In contrast to other hydrogel-based technologies, the hydrogel in Epitomee capsule is in the form of particles that absorb water to form a triangular gel scaffold that acts in the stomach with a significantly lower gel load than other devices (i.e., 0.3 g per dose in Epitomee vs. >2.25 g per dose in other hydrogel-based devices) [30]. The Epitomee capsule volume is relatively low; the large outer dimension of the scaffold maximizes gut-brain axis stimulation and eventually disintegrates above pH 6.5. Once the scaffold has disintegrated, the gel particles clear naturally. Thus, in contrast to other hydrogel-based technologies, there is no hydrogel burden in the small intestine requiring excretion. This may explain why the proportion of participants experiencing gastrointestinal AEs in the present study, assessed as related to the investigational device, was similar between the groups (Epitomee, 26.8%; placebo, 31.9%; $p = 0.3609$). By contrast, in a study of another hydrogel-based technology, the proportion of participants with gastrointestinal AEs, probably or possibly related to treatment, was significantly higher in those assigned to the device than to placebo (37.7% vs. 27.5%; $p = 0.025$) [30]. Gastrointestinal events included diarrhea, abdominal distention, infrequent bowel movements, constipation, abdominal pain, and flatulence [30].

As for comparing treatment efficacy, the Food and Drug Administration (FDA) noted a difference between US and European Union study populations for the other hydrogel device [31]. Given that RESET was conducted exclusively in the United States, the comparison here is limited to United States. Accordingly, the mean difference in percent weight loss between the other hydrogel device treatment group and its placebo group for the pooled US population was -1.5% (95% CI: -3.16% to 0.16%), whereas the mean difference between the Epitomee treatment group and its placebo group was -1.9% (95% CI: -3.3% to -0.6%).

Treatment decisions are based on a clinical judgment of the potential benefits of an intervention compared with the potential for harm, considering the participant's health status and risk of adverse outcomes. Antiobesity medications and bariatric surgery are treatment options for individuals with overweight or obesity as an adjunct to lifestyle intervention; however, side effects and contraindications may influence decisions to prescribe these interventions [32]. The Epitomee capsule is a non-systemic weight-loss device with a mechanical mechanism of action; therefore, there is low risk of drug interactions or systemic side effects. Therefore, it may be a suitable option for individuals with overweight or obesity as an early intervention to attain moderate weight loss or for individuals with complicated medical histories and medication regimens that create numerous contraindications or potential interactions. However, because of its mechanism of action, the Epitomee capsule should not be used in participants with altered stomach anatomy or function (e.g., prior gastric sleeve or gastric bypass, gastroesophageal reflux disease, or gastroparesis).

RESET has several potential limitations. Although the study enrolled a sample that was broadly representative of US adults with overweight and obesity, there are some limits to the generalizability of the results. For example, individuals with a BMI of greater than 40 kg/m^2 and those with type 2 diabetes were excluded from the trial; therefore, the efficacy of the Epitomee capsule has not been

established in these populations. Additionally, RESET investigated the efficacy and safety of Epitomee for weight loss over a relatively short duration (i.e., 6 months). A longer-term evaluation of the safety and efficacy of the Epitomee capsule is needed. In addition, changes in cardiovascular risk factors and laboratory results to assess efficacy were not described herein. Future publications addressing these outcomes are needed in order to provide a comprehensive understanding of the efficacy of the Epitomee capsule. Subgroup analyses, including of participants with lower versus higher BMI values, of individuals with and without prediabetes, and of people from different ethnic and racial groups, are limited owing to sample size.

In conclusion, the Epitomee capsule demonstrated efficacy over placebo as an adjunct to high-intensity lifestyle intervention for weight loss in individuals with overweight or obesity. Epitomee was well tolerated and had a favorable safety profile, with no device-related SAEs. This risk-benefit profile suggests that Epitomee would be most suitable as an early intervention to attain moderate weight loss or have potential broader application in individuals with a BMI of 27.0 to 40.0 kg/m^2 who are seeking nonpharmacological treatment for overweight or obesity. 

AUTHOR CONTRIBUTIONS

Jamy D. Ard contributed to the investigation, writing the original draft, and reviewing and editing the draft. Donna H. Ryan contributed to the conceptualization, writing the original draft, and reviewing and editing the draft. Patrick M. O'Neil contributed to the methodology, investigation, resources, and reviewing and editing the draft. Robert F. Kushner contributed to the conceptualization, methodology, investigation, and reviewing and editing the draft. Holly R. Wyatt contributed to the investigation and reviewing and editing the draft. Harold E. Bays contributed to the investigation and reviewing and editing the draft. Frank L. Greenway contributed to the investigation and reviewing and editing the draft. John M. Jakicic contributed to the investigation and reviewing and editing the draft. Sharon Leonard contributed to the supervision of the study. Yael Kenan contributed to the conceptualization, methodology, investigation, data curation, reviewing and editing the draft, visualization, supervision, and project administration. Eti Ganon-Elazar contributed to the investigation, data curation, reviewing and editing the draft, visualization, and data administration. Thomas A. Wadden contributed to the investigation, resources, and reviewing and editing the draft.

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CONFLICT OF INTEREST STATEMENT

Jamy D. Ard has received grant support from Nestlé Healthcare Nutrition, Eli Lilly and Company, Boehringer Ingelheim, Epitee, United-Health Group R&D, KVK Tech, and WW International, Inc. (formerly WeightWatchers); consulting fees from Nestlé Healthcare Nutrition, Eli Lilly and Company, OptumLabs R&D, Novo Nordisk A/S, Intuitive, Regeneron, Brightseed, Level2, WW International, Inc., Amgen, and Boehringer Ingelheim; receipt of equipment, materials, drugs, medical writing, gifts or other services from KVK Tech, WW International, Inc., and Nestlé Healthcare Nutrition; and serves as president of the Obesity Society and an executive board member for the American Society for Nutrition Foundation. Donna H. Ryan has received consulting fees from Altimmune, Inc., Amgen, AstraZeneca plc, Biohaven, Boehringer Ingelheim, Calibrate, Carmot Therapeutics/Roche, CinRx Pharma, Curax Pharmaceuticals LLC, Epitee Medical Ltd., Fractyl Health, Gila Therapeutics, Eli Lilly and Company, Nestlé Healthcare Nutrition, Novo Nordisk A/S, Scientific Intake, Structure Therapeutics, Wondr Health, and Zealand Pharma; payment or honoraria for lectures, presentations, speakers bureaus, and manuscript writing or educational events from Novo Nordisk A/S and Eli Lilly and Company; has participated on a data safety monitoring board or advisory board for Eli Lilly and Company, Rhythm Pharmaceuticals, and CinRx Pharma; and holds stock options for Epitee Medical Ltd., Calibrate, Roman Pharma, Scientific Intake, and Xeno Pharmaceuticals. Patrick M. O'Neil has received grant support from Epitee Medical Ltd., Novo Nordisk A/S, and Eli Lilly and Company; consulting fees from Novo Nordisk A/S; participated on an advisory board for Novo Nordisk A/S; and has an unpaid leadership or fiduciary role for the Diabetes Initiative of South Carolina. Robert F. Kushner has received grant support from Epitee Medical Ltd.; participated on a data safety monitoring board or advisory board for Novo Nordisk A/S, Eli Lilly and Company, Boehringer Ingelheim, Structure Therapeutics, Altimmune, Regeneron, and Weight Watchers; and holds a leadership or fiduciary role on the American Board of Obesity Medicine. Holly R. Wyatt has received grant support from Epitee Medical Ltd., General Mills, Inc., Novo Nordisk A/S, Gelesis, and the National Cattlemen's Beef Association; royalties or licenses from State of Slim: Fix Your Metabolism and Drop 20 Pounds in 8 Weeks on the Colorado Diet (book), IP owned by Shakabuku LLC, and IP licensed to University of Colorado; consulting fees from Gelesis; honoraria from the Cardiometabolic Health Conference and the Institute for Medical and Nursing Education; holds a patent issued or pending for Energy Gap; and holds stock or stock options for Shakabuku LLC (equity ownership interest), Dr. Holly LLC (equity ownership interest), and Roman Pharma. Harold E. Bays has received grant support from 89bio, Inc., Alon Medtech/Epitee Medical Ltd., Altimmune, Amgen, BioAge Labs, Boehringer Ingelheim, Carmot Therapeutics, Chorus/BioAge Labs, Eli Lilly and Company, Evidera, Kallopye, Novartis, Novo Nordisk A/S, Pfizer Inc., Regeneron, Satsuma Pharmaceuticals, Selecta, Shionogi, Skye Bioscience/Bird Rock Bio, Veru, Viking Therapeutics, and Vivus; consulting fees from 89bio, Inc., Altimmune, Amgen, Boehringer Ingelheim, Kiniksa Pharmaceuticals, HighTide Therapeutics, Eli Lilly and Company, Novo Nordisk A/S, Regeneron, Veru, Zomagen Biosciences, and ZyVersa Therapeutics;

participated on an advisory board for Epitee Medical Ltd., Altimmune, Novo Nordisk A/S, Boehringer Ingelheim, and Kiniksa Pharmaceuticals; and serves as chief science officer and president-elect of The Obesity Medicine Association. Frank L. Greenway has received grant support from Epitee Medical Ltd.; consulting fees from Altimmune, DexCom, Basic Research, and NovMetaPharma; support for meeting attendance from Biohaven; and holds patents issued or pending (US 11,534,442, US 11,058,662, US 10,897,921, US 10,507,194, US 9,999,601, US 8,334,000, US 7,709,031, US 17/245,538, and US 15/565,367); and stock or stock options from Pep19, Slim Health Nutrition, Inc., Rejuvenate Bio, Energesis Pharmaceuticals, Ketogenic Health System, GATC Health, and Uplifting Results Inc. John M. Jakicic has received grant support from Epitee Medical Ltd. and the National Institutes of Health; consulting fees from Scientific Advisory Committee for Wondr Health; and holds a volunteer leadership position at the American College of Sports Medicine. Sharon Leonard has received grant support from Epitee Medical Ltd. and Eli Lilly and Company; consulting fees from Epitee Medical Ltd. and Eli Lilly and Company; payment or honoraria for lectures, presentations, speakers bureaus, and manuscript writing or educational events from Epitee Medical Ltd. and Eli Lilly and Company; and support for attending meetings and/or travel from Epitee Medical Ltd. and Eli Lilly and Company. Yael Kenan is an employee of Epitee Medical Ltd. and holds stock or stock options. Eti Ganon-Elazar is an employee of Epitee Medical Ltd. and holds stock options. Thomas A. Wadden has received grant support, on behalf of the trustees of the University of Pennsylvania, from Eli Lilly and Company, Epitee Medical Ltd., and Novo Nordisk A/S and has served on scientific advisory boards for Eli Lilly and Company, Novo Nordisk A/S, and WW International, Inc.

DATA AVAILABILITY STATEMENT

At this point, the dataset used in this study will not be available, as it is part of ongoing regulatory submissions in several jurisdictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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